Feasibility of utilizing near-infrared spectroscopy and peripheral arterial tonometry to detect subclinical microvascular dysfunction in lower-limbs of patients with end-stage kidney disease

by

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Abstract

Cardiovascular disease stands as the primary cause of death among the population with dialysis-dependent end-stage kidney disease (ESKD). A significant portion of the ESKD population is diagnosed with peripheral arterial disease (PAD). The current clinical guidelines for PAD are considered insufficient for proper screening and management of individuals with ESKD. Microvascular dysfunction may precede the large vessel blockages characteristic of PAD and is a potential target for early detection and treatment. We assessed the feasibility (acceptability, interpretability, technical difficulty) of using near-infrared spectroscopy (NIRS) in the lower limb (tibialis anterior), and peripheral arterial tonometry (PAT) to assess microvascular function. A priori, feasibility was defined ≤ 10% of tests complicated by these domains. We also explored the reliability and validity of NIRS compared to the referent test of brachial hyperemic velocity-time integral (VTI). Fourteen individuals receiving hemodialysis (HD) and twenty-one healthy controls participated. Suprasystolic blood pressure (50mmHg above systolic blood pressure) was applied to induce arterial occlusions in the forearm and calf. The occlusion tests in the calves were terminated due to discomfort in four individuals in the HD group (i.e., 28%). Of the eleven individuals in the HD group who underwent NIRS tests, the data from two (i.e., 18%) were uninterpretable, while no data were missed due to technical issues. Therefore, within the current parameters, these procedures are not feasible in individuals with ESKD. In those with complete data in the HD group (N=9), NIRS parameters had moderate to high intraclass correlations, showing good test-retest reliability. Correlation analysis between brachial VTI and calf muscle oxygen consumption ($mVO_{2\%}$) measured by NIRS, and PAT was r=-0.43, p=0.21 and r=0.11, p=0.79 in the HD group, and r=0.19, p=0.41 and r=0.25, p=0.44 in the control group. The findings from this study provide information for determining the sample size required for

future diagnostic studies to develop more sensitive and accurate tests for vascular function in the population with ESKD.

Preface

This thesis is an original work by Ilhae Bok. The embedded research project, “Feasibility of utilizing near-infrared spectroscopy and peripheral arterial tonometry in lower-limbs of patients with end-stage kidney disease”, received research ethics approval from the University of Alberta Health Research Ethics Board (Pro00115743), Aug 15, 2022. No part of this thesis has been previously published.

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List of Abbreviations

ABI – Ankle-brachial index

ACC – American College of Cardiology

AHA – American Heart Association

AI – Augmentation index

A.U – Arbitrary unit

BA – Brachial Artery

CKD – Chronic kidney disease

CTA – Computed tomography angiography

CV – Coefficient of variation

CVD – Cardiovascular disease

DUS – Duplex Ultrasound

ESKD- End-Stage kidney disease

FMD – Flow-mediated dilation

eGFR – Estimated glomerular filtration rate

GFR – Glomerular filtration rate

HD – Hemodialysis

HHb – Deoxygenated hemoglobin

IC – Intermittent claudication

ICC – Intraclass correlation

LDF – Laser Doppler Flowmetry

LDL – Low-density lipoprotein

PAT – Peripheral arterial tonometry

MAC – Medial arterial calcification

MRA – Magnetic Resonance Angiography

mVO_2: Muscle oxygen consumption

NIRS – Near-infrared spectroscopy

NO – Nitric Oxide

O_2Hb- Oxygenated hemoglobin

PA – Popliteal artery

PVD – Peripheral Vascular Disease

RHI – Reactive Hyperemia Index

ROS – Reactive oxygen species

TBI – Toe-brachial index

$TcPO_2$ – Transcutaneous oximetry

tHb – Total hemoglobin

VTI – Velocity time integral

Chapter I: Introduction

1.1 Background

Chronic kidney disease is a condition identified by either the presence of kidney damage markers like proteinuria or a reduction in kidney function for more than 90 days.[1] The management of chronic kidney disease is to control the key risk factors for the disease progression such as hypertension, proteinuria, and diabetes.[2] However, the impairment of kidney function is irreversible, and an individual may experience further decline in kidney function that requires kidney transplantation or dialysis modalities to replace the failed kidney function.[3] This stage of the disease is referred to as end-stage kidney disease (ESKD)and approximately 6,000 individuals are newly diagnosed with ESKD every year in Canada with an annual cost of care of $1.8 billion.[4,5] ESKD is associated with a high risk of cardiovascular morbidity and mortality due to heightened inflammation, vascular calcification, oxidative stress, and the dialysis treatment.[6] In individuals with ESKD, cardiovascular-related mortality is the leading cause of death, which is 4-20 times higher than in individuals with normal kidney function.[7,8]

Peripheral arterial disease (PAD) is defined as atherosclerotic occlusion of peripheral arteries located in lower- or upper-extremities.[9] In the population with ESKD, PAD is one of the most common cardiovascular complications that over a quarter of the population is affected by (25-46%).[10] Lower-limb complications are common in individuals affected by PAD, including ischemic tissue loss such as foot ulcers and gangrene, infections, and nontraumatic amputation.[11] Individuals affected by both PAD and ESKD have strikingly high frequency of non-traumatic lower limb amputation and ulceration 74.9 per 1,000 patient-years, with a corresponding adjusted hazard ratio of 10.36 (95% CI, 8.83-12.16) compared to individuals with preserved kidney function without PAD.[12]

Despite these significant risks and adverse outcomes, the current clinical guidelines for PAD are considered insufficient for the proper screening and management of individuals with ESKD.[1,13,14] First, PAD itself is often underdiagnosed as more than 85% of affected individuals exhibit no discernable symptoms of claudication: pain in the extremities at physical exertion. [15,16] The ankle-brachial index is the first line of screening tools recommended by the guidelines owing to simple non-invasive operation and good sensitivity in diagnosing PAD (83-99%).[17] However, medial arterial calcification being extremely common in individuals with ESKD, falsely deviate the value, lowering the sensitivity of the ankle-brachial index to 49%.[18,19] The alternative tool of a toe-brachial index is recommended in the population with incompressible arteries, but its sensitivity is still questionable when used in individuals with CKD (45%) and individuals receiving HD (sensitivity = 45.2%).[20,21] The American Heart Association and American College of Cardiology guidelines recommend using computed tomographic angiography, magnetic resonance imaging or duplex ultrasound as diagnostic imaging tools for PAD.[22] However, these tools have limitations when applied to individuals with ESKD. The potential contraindications associated with the use of contrast-based agents in individuals with ESKD, combined with high operational costs and the need for trained professionals and expensive equipment, significantly reduce their feasibility for routine clinical use.[23,24]

Querfeld et al.[25] highlighted that the currently used diagnostic tools for PAD predominantly concentrate on stenosis or obstructions in macrovasculature (300μm), and are inadequate in detecting and addressing microvascular dysfunction or injury. This observation aligns with findings by Beckman et al.[26], who demonstrated that the presence of microvascular disease can increase the risk of amputation by 3.7 times, even without a diagnosis of PAD. The reduced efficacy of surgical intervention for PAD is observed in individuals with ESKD which

may be attributable to the fact that these procedures predominantly target the large conduit arteries.[27] Combined, proper identification of the microvascular impairments may improve clinical outcomes and reduce the risks of lower-limb complications in individuals with ESKD.

Compared to currently used diagnostic tools, continuous-wave near-infrared spectroscopy (NIRS) and peripheral arterial tonometry (PAT) are considered as non-invasive, cost-effective, and operator-independent tools that can assess microvascular function.[28,29] Prior research has highlighted NIRS' ability to detect alterations in microvascular hemodynamics during dynamic measurements such as exercise or post-occlusive hyperemia, showing its potential in diagnosing PAD.[30,31] Furthermore, parameters derived from PAT are observed to hold prognostic significance for cardiovascular complications across a wide range of clinical populations.[32-34] However, the existing body of evidence regarding the utility or feasibility of NIRS/PAT in assessing microvascular function in the lower limbs of individuals with ESKD remains limited.[35] Furthermore, preliminary data must be obtained to conduct studies that examine NIRS/PAT's ability to screen subclinical manifestations of PAD and detect microvascular dysfunction or injury in individuals with dialysis-dependent ESKD.

1.2 Purpose

The purpose of this study is to investigate the feasibility of utilizing NIRS/PAT-based vascular function tests in individuals with dialysis-dependent ESKD.

1.3 Hypothesis

We hypothesize that 1) the selected non-invasive tests of microvascular function (NIRS and PAT) will be feasible to obtain and well-tolerated by the individuals with dialysis-dependent ESKD, as measured by *a priori* criteria. 2) The NIRS and PAT measured microvascular

parameters will correlate (r >0.7) with the referent test (VTI), 3) NIRS and PAT will differ significantly between individuals on HD versus the control group, 4) The NIRS and PAT measured parameters will have good test-retest reliability (ICC >0.7) in the HD group. 5) The vascular parameters for individuals in the HD group with abnormal ABI (<0.9, or ≥1.4) and/or TBI (<0.70) will show significantly slower post-occlusive oxyhemoglobin recovery as measured by NIRS, and lower reactive hyperemia index by PAT compared to the control group. 6) For individuals in the HD group with abnormal ABI (<0.9, or ≥1.4) and/or TBI (<0.70), the vascular parameters will correlate (r>0.7) with the physical activity level (step count per day).

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Chapter II: Literature Review

2.1 Chronic Kidney Disease and Renal Replacement Therapy

2.1.1 Introduction

The kidney is a vital organ that regulates fluid volume, electrolyte, acid-base balance, and several hormones to ensure homeostasis. Erythropoietin is a glycoprotein hormone produced by the interstitium between renal tubular cells, which is responsible for red blood cell production in the bone marrow.[1] The renin-angiotensin system primarily regulates sodium and blood pressure through the release of renin. At the same time, metabolic regulation is achieved by controlling water and solute transport and the excretion of metabolic waste products through the glomeruli, renal tubules, and/or nephrons. The kidney also yields 1,25-dihyroxyvitamin D, the active form of vitamin D's and essential for regulation of the effects of calcium and phosphorus metabolism, bone health, and the regulation of parathyroid function.[2]

The estimation of kidney function is done by evaluating the rate of elimination of specific biomarkers [termed estimated glomerular filtration rate (eGFR)] and by measuring the urine albumin to creatinine ratio. The conventional biomarker used to estimate kidney function is the blood serum concentration of creatinine, which is expressed in mL per minute and corrected by standard body surface area of 1.73m^2.

The level of eGFR indicates kidney function and is interpreted in the clinical context to identify kidney disease in an individual.[3] Moreover, excretion ratio of urinary albumin to creatinine represents the glomerular endothelial function and is a predictor of cardiovascular and renal events independent to eGFR.[4,5] Individuals with kidney disease are classified based on clinical practice guidelines by Kidney Disease Improving Global Outcomes[6], including further

stratification according to the severity of eGFR impairment and the urine albumin to creatinine ratio.

2.1.2 Chronic Kidney Disease and End-stage Kidney Disease

Chronic kidney disease (CKD) is a significant global health concern that affects more than 10% of the population worldwide.[7] It is defined as an eGFR under 60ml/min/1.73m^2 or the presence of proteinuria for more than 90 days.[6] The main causes of CKD are hypertension and diabetes, particularly in upper- and middle-income countries.[8] These two leading causes of CKD are also becoming prevalent in low-income countries with the rapid urbanization and corresponding lifestyle changes, contributing to a worldwide increase in the CKD population.[9] In Canada, at least 4 million people have CKD, and adding an estimated annual cost of $40 billion to the healthcare system.[10,11]

The mainstay of CKD management is to control key risk factors for CKD progression, such as hypertension, proteinuria, and diabetes. However, with the irreversible nature of kidney disease, 18% of individuals with mild-to-moderate CKD in stage 3 experience a greater than 4 mL/min/1.73m^2 drop in eGFR per year, with approximately 6,000 new cases of end-stage kidney disease (ESKD) diagnosed annually in Canada.[12,13]

ESKD is when the kidney can no longer independently sustain homeostasis and is defined as an eGFR less than 15 mL/min/1.73m^2.[14] Management of ESKD is limited to kidney transplantation or renal replacement therapy, commonly referred to as dialysis. The Canadian Society of Nephrology guidelines[15] recommends beginning renal replacement therapy once the patient's eGFR falls into a range of 6-8 ml/min/1.73 m^2.

2.1.3 Hemodialysis as Renal Replacement Therapy

The majority (~70-80%) of individuals receiving dialysis in Canada are treated with intermittent facility-based or "in-center" hemodialysis (HD) as a form of the renal replacement therapy. In-center HD requires medical supervision during the 3-5 hour sessions, three times per week.[13,16] HD utilizes a diffusive mechanism to passively remove solutes via concentration gradients between the blood and the dialysate. Moreover, the machine-generated hydrostatic pressure gradient across the dialyzer membrane removes fluid via ultrafiltration and solute removal via a convective mechanism.[17]

Despite the administration of dialysis, it is incapable of fully replacing the reduced kidney function. While the removal of uremic toxins via dialysis is a major therapeutic target to improve the risk of CVD-related morbidity and mortality in ESKD populations[18], inadequate dialysis results in abnormal levels of uremic toxins and contributes to a higher risk of CVD in individuals with ESKD.[19,20] Additionally, the current dialysis technique has limitations in eliminating certain protein-bound uremic toxins, like indoxyl sulfate, which can lead to cardiovascular calcification and changes in mineral metabolism.[21,22]

Another goal of each HD session is to manage the individual's fluid and sodium level. Inappropriate fluid and sodium management are associated with poorer clinical outcomes, including left ventricular hypertrophy, hypertension, chronic heart failure, ischemia, myocardial stunning, and hypertension.[23] Fluid removal during HD is prescribed based on the estimated dry weight of each individual, which is intended to keep the dialysis recipient normotensive while achieving the lowest possible extracellular fluid volume.[24] However, the intermittency and amplitude of volume fluctuation during the dialysis treatment imposes a significant hemodynamic stress on the patient and is considered a potent disease modifier.[25] Furthermore, the thermal gradient between dialysate and patient adds neurohumoral stress and

amplifies the burden.[25] In this manner, 25.6-28.3% of individuals with ESKD die within the early period of dialysis initiation (<120 days), while the 5-year mortality rate is 40-59%.[26,27] The overall survival rate of individuals on dialysis is 13-60% lower than the general healthy populations in the same age group.[28]

2.2 Increased Risk of Cardiovascular Disease in Chronic Kidney Disease

2.2.1 Introduction

With the pathology of CKD and CVD sharing various overlapping risk factors, individuals with ESKD have a greater risk of cardiovascular morbidities such as congestive heart failure, myocardial infarction, and peripheral arterial disease.[29] Due to shared CVD comorbidities, the proportion of CVD-related deaths increases with decreasing eGFR, making it the most common cause of death in the population with decreased eGFR (<60ml/min per $1.73m^2$).[30] Multiple overlapping conditions such as hyperuricemia, dyslipidemia, obesity, hypertension, and diabetes are the most common independent risk factors for developing CKD.[31]

While conventional risk factors such as hypertension, diabetes, or dyslipidemia are common in patients with CKD, they do not fully explain the high prevalence of cardiac events and CVD-related mortality in ESKD.[32,33] CKD-specific pathological mechanisms, such as endothelial dysfunction, increased oxidative stress, uremic toxicity, phosphorus calcium imbalance, and anemia can damage to both the micro- and macro-vasculature, contributing to adverse cardiovascular outcomes.

2.2.2 Risk Factors and Mechanisms of Vascular Damage in Chronic Kidney Disease

Individuals with ESKD are in a chronic inflammatory state. Inverse correlations between GFR and levels of proinflammatory cytokines, including C-reactive protein, interleukin-1,

interleukin-6, tumor necrosis factor, or the fibroblast growth factor 23 have been reported.[34,35] Individuals are exposed to further risks of inflammation once they initiate dialysis due to the retention of uremic toxins, the exogenous factors from treatments (dialysis membranes and central venous catheters), tissue hypoxia, sodium, and fluid overload.[36] Moreover, hepcidin, a regulator of iron hemostasis, increases in ESKD due to decreased renal clearance and inflammation, reducing blood iron availability. This leads to renal anemia and increased reactive oxygen species (ROS) formation.[37,38] In the individuals with ESKD, the increase in ROS and free radicals produced from disrupted mitochondrial respiration imposes increased oxidative stress contributing to mitochondrial dysfunction, endothelial cell injury, and apoptosis.[39,40]

The endothelial nitric oxide (NO) synthase, primarily responsible for vasodilation and protection against cell proliferation, is depressed in the CKD population.[41] The production of L-arginine, an essential precursor for NO, is reduced to 40% of normal levels with the degeneration of kidney function, negatively affecting NO bioavailability.[42] Also, the decrease in GFR leads to the accumulation of uremic toxins, such as asymmetric dimethylarginine, promotes apoptosis, and directly inhibits endothelial NO synthase activity.[43,44] Another uremic toxin, indoxyl sulfate, negatively affects endothelial NO synthase activity and further contributes to ROS formation.[45,46]

Dyslipidemia greatly contributes to CVD development and is particularly evident in individuals with ESKD who receive dialysis.[47] People with ESKD receiving HD exhibit elevated serum triglyceride levels and lipoprotein abnormalities and, in particular, elevated low-density lipoprotein (LDL).[48,49] Combined with elevated oxidative stress, increased LDL particles are more likely to be oxidized (Ox-LDL) and promote monocyte infiltration and adhesion to glomerular endothelial cells, inducing cell apoptosis.[50] The Ox-LDL also directly inhibits endothelial NO synthase activity and further reduces NO availability.[51] The prescription of LDL

lowering medication such as statin is one of the standard pharmacological interventions to lower CVD risk.[52] However, several large randomized trials have reported that the benefits of lipid-lowering interventions, such as statins, have not been demonstrated in dialysis-dependent individuals.[53] This suggests that individuals with ESKD have a significant risk of non-atherosclerotic impairment in vascular function (i.e., ROS formation, NO reduction, vascular calcification) secondary to the high level of atherosclerotic risk.[54]

The parathyroid hormone is upregulated in the early stages of CKD to compensate for the kidney's impaired phosphorus excretion.[55] In the later stages of CKD, the degenerating phosphorus excretion coupled with hypocalcemia due to impaired renal production of vitamin D3 ultimately induces maladaptive parathyroid hormone secretion and causes secondary hyperparathyroidism.[56,57] The imbalances in calcium and phosphorus contribute to the calcification of blood vessels as it alters the phenotype of vascular smooth muscle cells to osteogenic, increasing mineral deposition and cell degradation.[56]

2.2.3 Physical Inactivity as an Additional Risk Factor for Vascular Dysfunction

The level of physical activity is considered a major modifiable risk factor in chronic disease management.[58] Lack of physical activity, or physical inactivity even for as short as five days, can increase insulin resistance, induce dyslipidemia, and impair microvascular function.[59] Similarly, the association between reduced level of physical activity and increased risk of cardiovascular events is consistently reported in CKD.[60,61] Several previous studies examined level of physical activity as an intervention and reported improvements in markers of vascular function. For instance, Correa et al.[62] implemented ~50 minute intradialytic exercise in individuals receiving HD three sessions per week for 12 weeks, and reported improved NO bioavailability and reduced levels of asymmetric dimethylarginine. Similarly, Rus et al.[63] used

daily handgrip exercise for 30 minutes in 8 weeks duration as an intervention and reported enhanced endothelium-dependent dilation.

A prospective cohort study by Ricardo et al.[64] examined 3006 individuals with moderate CKD and showed an elevated risk of atherosclerotic events in those individuals with low levels of physical activity In ESKD, physical function is negatively affected by CKD-specific conditions such as uremic sarcopenia, mineral bone disorder, or chronic inflammation, which contribute to reduced levels of physical activity.[65] The levels of physical activity decrease with CKD progression, and decline even further once the individual starts maintenance dialysis.[66,67]

A large cohort study by Johansen et al.[68], which incorporated 1547 individuals on maintenance dialysis, showed that self-reported PA was lower compared to the healthy population below the 25th percentile in every age group. Another large cohort study with 1611 individuals on dialysis also showed that the majority the cohort are categorized under either no- (45.5%) or low- (37.1%) intensity self-reported physical activity.[69] Other studies that utilized accelerometers also reported consistently low level of physical activity in ESKD.[70-72] In a recent retrospective study by Harada et al.[73], the habitual level of physical activity (step/day) was significantly lower in dialysis-dependent individuals compared to the healthy controls, and the level of physical activity decreased further in those individuals who developed PAD. Combined, these studies demonstrate that the level of physical activity is likely reduced in CKD, and this would contribute to impaired vascular function and increased risk of CVD.

2.2.4 Peripheral Artery Disease and Chronic Kidney Disease

Peripheral artery disease (PAD) is defined as partial or complete atherosclerotic obstruction of peripheral arteries located in lower- or upper-extremities.[74] The pathophysiology

of PAD includes arterial lesions or stenosis induced by atherosclerosis, thrombosis, noncardiac emboli or inflammation.[75] The presentation of PAD varies between individuals, ranging from asymptomatic despite the progression, pain or discomfort following an exertion or intermittent claudication (IC), and functional impairment and to critical leg ischemia leading to limb amputations.[76,77]

Globally, the prevalence of PAD is 5-12% in the age group over 40.[78] With previously discussed factors affecting the vascular function, people with ESKD have a threefold higher prevalence of PAD, which increases with the severity of CKD.[79,80] Therefore, over a quarter of ESKD population (25-46%) is diagnosed with PAD.[81,82] While PAD alone increases the mortality rate by two- to four-fold compared to the healthy population, when the individuals have both CKD and PAD, the mortality rate increases 1.5- to three-fold compared to individuals with either disease alone.[83-85] Similarly, a 3-year follow-up study that looked at the cohort of 3,109 individuals reported a greatly increased risk of CVD mortality in the individuals with both CKD and PAD; the adjusted relative risks of CVD mortality in individuals with non-dialysis CKD, PAD alone, and both diseases are 1.79 (95% CI: 1.24–2.59), 1.95 (95% CI: 1.28–2.96), and 4.34 (95% CI: 2.97–6.34), respectively, compared to the group without neither PAD and CKD.[86]

2.2.5 Lower-limb Complication and Chronic Kidney Disease

Lower-limb complications (LLC), including ischemic tissue loss such as foot ulcers and gangrene, infections, and in severe cases, nontraumatic amputation, are common in individuals with PAD.[87] Although PAD is considered as a key manifestation of atheleroscleroris and is a strong predictor of systemic cardiovascular events such as myocardial infarction, stroke, or

coronary artery disease[88,89], it is noticed that PAD does not relate as strongly as to the risk of LLC.[90]

Behroozian and Beckman[91] argue that the changes in the index of blood pressure of large conduit arteries (ABI) do not appropriately reflect the microvascular dynamics. The currently used diagnostic tools and treatments for PAD are focused on the macrovasculature and overlook microvascular dysfunction (blood vessels <300 μm).[92] As a result, the microvascular disease is undertreated, and significantly increases the risk of amputation when combined with PAD, as it acts as a potent risk amplifier. Compared to the individuals with neither disease, those with both PAD and microvascular disease have a much higher risk of amputation (HR:22.7 [95% CI, 18.3–28.1]) than those with PAD alone (HR:13.9 [95% CI, 11.2-17.1]).[90]

Individuals with ESKD face reduced efficacy of surgical interventions for PAD, which may be partly due to microvascular dysfunction and injury. Currently, surgical revascularization procedures primarily target large conduit arteries to improve oxygen tension in distal tissue while neglecting the microvasculature.[90] A retrospective study found that 59% of patients with ESKD still required amputation despite a successful surgical revascularization without major procedural complications.[93] Additionally, individuals with ESKD had poorer outcomes in terms of mortality, limb salvage rate, and graft survivability compared to those without ESKD.[93] A higher rate of amputation is also reported in dialysis-dependent individuals (29%) compared to those with preserved kidney function (10%) within a year after a surgical intervention.[94] Overall, these findings suggest that current clinical tools used for diagnosing PAD may be inadequate in detecting and treating microvascular dysfunction or injury, which could play a role in the increased risk of adverse outcomes for patients with ESKD. Proper identification of these

impairments has the potential to improve clinical outcomes and reduce the risks of LLC in ESKD.

2.3 Current Non-invasive Diagnostic Tools for Peripheral Vascular Dysfunction

2.3.1 Current Clinical Tools for Peripheral Arterial Disease

Current clinical guidelines by the American College of Cardiology (ACC) and American Heart Association (AHA) recommend that diagnostic procedures for PAD begin with a medical history, review of symptoms, and physical examination.[95] The review of medical history and symptoms includes a key clinical symptom of claudication, defined by fatigue, discomfort, cramping, or pain of vascular origin of muscles in the lower extremities induced by exercise and relieved by rest.[95] However, individuals with PAD are often asymptomatic without the classic symptom of extremity pain during exertion or typical claudication; less than 15% of individuals with confirmed PAD manifest claudication.[96] A recent meta-analysis showed that a significant proportion of individuals with CKD or ESKD are potentially underdiagnosed due to the asymptomatic nature of PAD when relying solely on the self-reported history of claudication.[97]

Ankle-brachial Index

The ankle-brachial index (ABI) is a commonly used clinical test for evaluating PAD. It assesses changes in blood pressure in the large conduit arteries of the lower limb. ABI is calculated by dividing the highest ankle systolic pressure by the highest arm systolic pressure using a pneumatic cuff.[98] This non-invasive and cost-effective tool is well-established and widely accessible, making it a next line screening tool for PAD.

The severity of vascular stenosis in PAD is directly associated with a decrement in ABI. ABI values also provide prognostic information on CVD-related risk, morbidity, and

mortality.[99,100] An ABI value of 1.00-1.40 is considered normal, and a value <0.90 is considered abnormal.[95,101] A structured review including 1,593 limbs in individuals without CKD and between the ages of 35-94 reported that the ABI value used for the clinical diagnosis of PAD has good sensitivity (83-99%) when compared to non-invasive modalities such as computed tomography angiography, magnetic resonance angiography, and Duplex ultrasound.[102]

However, the diagnostic accuracy of using ABI in the ESKD population is not well established. Medial arterial calcification (MAC), which is common in the population with CKD (23%) and ESKD (41%) due to phosphorus and calcium imbalance-induced vascular calcification, makes the ankle arteries incompressible and falsely elevates ABI.[79,103] With inflated ABI values, the sensitivity for PAD is decreased to 49% when using the same clinical abnormality cut-off value (ABI <0.90) in individuals with CKD compared to Duplex ultrasound.[104] It is recommended that individuals with MAC exhibiting abnormally high ABI (≥1.40) are screened using an alternative diagnostic tool, such as the toe-brachial index.[105] However, individuals with only mild MAC may present with normal ABI (1.00-1.40), increasing the false-negative rate of ABI for diagnosing PAD by ~30%.[101,106] Furthermore, the current guidelines including ACC/AHA[107] and the United States Preventive Services Task Force[108] do not recommend using ABI if the individual is asymptomatic.

Apart from using ABI to diagnose PAD, the recent literature highlights the disparity in ABI values in individuals with more severe clinical manifestation of PAD which includes chronic ischemic rest pain, ulcers, or gangrene. Shishebor et al.[109] examined 237 individuals who underwent surgical revascularization and reported normal ABI values in ≈29%. Similarly, the multicenter study by Sukul et al.[110] showed that 24% of the individuals who received surgical

revascularization had normal pre-intervention ABI. Therefore, the use of ABI to diagnose PAD or to assess the level of vascular impairment in individuals with ESKD is not optimal.

Toe-brachial Index

Due to the inaccuracy of ABI in individuals with MAC or incompressible arteries, the current guidelines by AHA/ACC[107] and Trans-Atlantic Inter-Society Consensus[111] recommend toe-brachial index (TBI) as an alternative screening method for patients with ABI ≥1.40.[112] TBI utilizes toe blood pressure, which is relatively unaffected by the MAC, therefore alleviating under diagnosis owing to the falsely elevated ankle blood pressure.[113] The TBI is calculated as the ratio of the highest great toe or second toes' systolic pressure to the highest brachial systolic pressure. A value ≤0.70 is considered abnormal, while TBI in healthy populations is between 0.94-0.98.[114,115] The high sensitivity of TBI for detecting PAD is reported in a range of individuals with different clinical conditions: critical limb ischemia (92%), elevated ABI (99%), diabetes (100%), and elevated risks of PAD (71%).[116-119] However, the sensitivity of TBI is questionable when used in individuals with CKD (45%) and individuals receiving HD (45.2%).[120,121]

Imaging modalities used in PAD

The current AHA/ACC guideline[107] recommends additional diagnostic anatomic assessments on individuals after the initial screenings (ABI/TBI) once they are suspected of PAD.

Computed tomography angiography (CTA) is one of the widely used imaging modalities to diagnose PAD. It uses an intravascular injection of a contrast agent during X-ray imaging that can subtract a picture of only the opacified arterial tree to detect vascular stenosis or lesions.[122]

CTA's diagnostic accuracy is well established, with a sensitivity of 89-99% and specificity of 83-97% for detecting stenosis over 50%.[123] However, the CTA imposes a risk of extra arterial puncture for the contrast agent, which can exacerbate the patient's vascular impairment.[124] Furthermore, ionized agents used for CTA can have a high osmolality that may induce acute kidney injury.[125] The ESKD-induced vascular calcification also causes artifacts for CTA imaging, which further limits its utility in the CKD population.[101,122]

Compared to CTA, magnetic resonance angiography (MRA) is a less invasive method using either time-of-flight or contrast-enhanced techniques to detect the movement of blood compared to static surrounding tissue.[123] Despite MRA's limitations due to low spatial resolution and motion artefact, MRA entails good sensitivity for PAD (79-99.5%) and specificity (64-99%).[123,126] The gadolinium-based contrast agents used for MRA may confer possible long-term deposition in the skin, bones, and brain.[127] The European Society of Urogenital Radiology and American College of Radiology guidelines suggest using Group II (macrocyclic agents gadobenate dimeglumine) gadolinium-based contrast agents rather than nonionic linear chelate agents in individuals with CKD 4 and 5 (<30ml/min/1.73m^2) in order to minimize the risk of nephrogenic systemic fibrosis.[128,129]

Duplex Ultrasound (DUS) is considered the gold standard for diagnosing PAD by Kidney Disease Improving Global Outcomes clinical guidelines. DUS is a combination of pulsed Doppler sonography and ultrasound B-mode imaging that can localize Doppler flow patterns and compare peak systolic velocities between stenosed and non-stenosed blood vessels.[130,131] Although DUS is time-consuming with high operator dependency, it is a first-line imaging modality as it is low-cost and avoids the complications of contrast agents or ionizing radiation.[132,133] However, unlike MRA or CTA, DUS lacks visualization of blood

vessels, and its quantitative accuracy decreases with the presence of arterial calcification due to weakened flow signals.[134]

2.3.2 Proposed Alternative Tools

Apart from the inherent limitations of current imaging modalities in individuals ESKD, these modalities are mainly designed to detect major stenosis in large conduit arteries.[92] As microvascular impairment is considered a significant contributor to the elevated risk of limb loss in ESKD and may remain undiagnosed and undertreated, researchers are exploring alternative tools to assess microvascular function.

Transcutaneous Oximetry

Transcutaneous oximetry ($TcPO_2$) is a non-invasive technique to measure microvascular function by measuring temperature-dependent gas diffusion from the microvasculature to the skin surface.[135] It utilizes a heated electrode (≈45C˚) that transmits heat to raise the skin temperature ≈43C, which abolishes factors affecting local circulation such as patient anxiety, pain, or arterial partial pressure of CO_2.[136] The electrode sensors can detect the O_2-diffusion based on the pressure gradient from capillary to avascular epidermis close to the skin surface.[137] Notably, the $TcPO_2$ method is influenced by the central arterial-O_2 content and local tissue perfusion, which are potential limiting factors in patients with CKD.[138] The ischemic state of microvasculature can be evaluated using $TcPO_2$; $TcPO_2$ under 30mmHg and 10mmHg is considered a severe and critical ischemic state, respectively.[139]

The AHA/ACC guidelines[107] recommend using $TcPO_2$ for diagnosing critical limb ischemia or lower limb arterial stenosis in individuals with currently diagnosed or potential PAD. Compared to the gold standard (CTA) for diagnosing PAD (≥50% arterial stenosis), the

delta decrease of $TcPO_2$ (resting baseline - post-exercise) showed good sensitivity (86%) and specificity (84%) using >15mmHg drop as a cutoff.[140] Compared to the healthy individuals, decreased $TcPO_2$ is reported in incident HD patients without PAD.[139] However, the reliability of $TcPO_2$ can be reduced in population with ESKD as edema or anemia may lead to the underestimation of $TcPO_2$, while chronic inflammation may lead to inflated $TcPO_2$ values.[137,141]

Laser Doppler Flowmetry

Laser doppler flowmetry (LDF) is a non-invasive technique proposed in 1980 for the evaluation of microcirculation and is widely used to detect arterial occlusion in postoperative settings.[142,143] The advantage of using LDF for measuring tissue perfusion is its extremely high temporal resolution (milliseconds) in the target area, which can detect fast changes during provocations.[144] Impaired LDF recovery values in response to post-occlusive reactive hyperemia are associated with CVD risk factors and mortality in individuals with ESKD.[145]

The optical property of tissue measured by LDF can be easily disrupted by slight movement. Therefore, LDF only allow assessments in static conditions.[144] In addition, the measuring depth of 0.5-1.0mm and volume of $1mm^3$ only allows examination of cutaneous microvascular blood perfusion in the dermis which lacks accuracy in mapping the regional microvascular dysfunction.[146] The LDF's intrinsic variability also presents challenges as LDF cannot distinguish between tissue blood velocity signals and changes in red blood cell concentrations. A tissue with venous stasis will have an increased concentration of red blood cells due to impaired outflow of blood and slowed velocity, potentially altering the LDF signal.[147] In conclusion, the current evidence for diagnostic accuracy of LDF-measured parameters for PAD is limited, especially in the population with ESKD, and therefore requires

further research.

Peripheral Arterial Tonometry

Peripheral arterial tonometry (PAT) is a non-invasive, fully automatic technique utilizing photoplethysmography to measure pulse wave amplitude in the fingers during and after forearm cuff occlusion.[148] The probe encloses the measured tissue with the sub-diastolic uniform pressure preventing venous pooling and reducing arterial wall motion; allowing it to examine small digital microvascular function.[149] An advantage of PAT is that it is fully automated and does not require technical expertise to obtain values. The PAT-index or reactive hyperemia index (RHI) is calculated as the peak pulse wave amplitude post cuff deflation divided by the baseline value prior to occlusion.[150] While there is no reference value for RHI, an RHI <2 arbitrary units (a.u) represents endothelial dysfunction, whereas higher RHI values are considered normal or improved endothelial function.[151] Large cohort studies by Schindler et al.[152] and Rubinshtein et al.[153] showed that low RHI is associated with an increased risk of adverse cardiovascular events. The baseline pulse wave amplitude is inversely related to mortality, but PAT-derived parameters' relationship to mortality in the general population is largely unknown.[154]

Flow-Mediated Dilation and Velocity-time Integral

Flow-mediated dilation (FMD) is a non-invasive technique that utilizes B-mode imaging on duplex ultrasound to assess endothelial vascular function in conduit arteries during hyperemic response.[155] The blood flow is increased during hyperemia following a release of a period of vascular occlusion. Transiently, the shear stress to the vascular walls elevates and stimulates endothelial NO release, resulting in endothelial-dependent dilation of the conduit

arteries. The comparison between the baseline diameter and maximal dilation yields FMD% change and represent one's endothelial function [(peak diameter – baseline diameter)/baseline diameter*100].[156]

Early work suggests a correlation between FMD% and coronary endothelial function.[157] FMD% has demonstrated prognostic values; a meta-analysis reported that a 1% increase in FMD was associated with an 8-13% reduction in the risk of cardiovascular events.[158,159] A series of studies consistently demonstrated impaired FMD in individuals with PAD compared to the healthy controls.[160-162] Observational studies reported that endothelial-dependent FMD significantly worsens in individuals with advanced CKD (stage 4-5).[41,80,163]

Velocity-time integral (VTI) is a measurement of the area under the velocity time curve during immediate reactive hyperemia following a brief period of vascular occlusion during the FMD assessment.[164] The metabolic vasoactive substances produced in the ischemic tissue distal during the occlusion of the conduit artery induces the dilation of the microvasculature. The extent of this microdialation prevails over the peripheral vascular resistance at the local tissue and induces sharp increase in blood flow immediately following the occlusion period as demonstrated by a large VTI. Therefore, the velocity profile (VTI) of the blood flow upsurge is considered a safe and cost-effective measure of microvascular function that is relatively less sensitive to body size compared to blood flow markers.[165-167]

Several studies have demonstrated VTI's predictive value for cardiovascular mortality and risk of cardiac events.[168,169] Similarly, impaired VTI was significantly associated with hospitalizations related to cardiovascular diseases and all-cause mortality in individuals receiving dialysis.[170] Anderson. et al.[171] demonstrated that heightened hyperemic VTI (>80cm)

was an independent predictor of adverse cardiovascular events in 1,578 healthy males with an average age of 49.4 years.

Though FMD's region of interest is large conduit arteries (brachial and popliteal arteries), VTI measured during FMD assessment is suggested to be an indicator of peripheral microvascular function as the reactive hyperemia response is highly dependent on the maximal limb vascular resistance.[172] Therefore, the evaluation of hyperemic flow is suggested for investigating microvascular function.[173,174]

Near-infrared Spectroscopy

Continuous wave near-infrared spectroscopy (NIRS) is a non-invasive tool that assesses microvascular function in the tissue of interest under various conditions, such as exercise tests and arterial occlusion.[175,176] It utilizes near-infrared wavelengths (700~1000 nm) of the electromagnetic spectrum to measure the changes in optical density in biological tissue, which is dictated by the Beer-Lambert Law on light scattering and absorption.[177,178] NIRS allows for the examination of oxygenation and changes in blood flow by tracking the concentration changes in oxygenated- (O_2Hb), deoxy-hemoglobin (HHb), and total-hemoglobin (tHb) in the tissue of interest.[179]

By implementing other techniques, such as cuff-induced ischemia, hyperemia, or exercise modalities, the NIRS signal can evaluate the O_2 delivery and O_2 utilization within the tissue.[176] For example, the cuff-induced ischemia eliminates the volumetric change of blood and allows the examination of oxygen consumption at the local tissue by analyzing the rate of the NIRS signal change.[180] The cyclic changes in the NIRS signal during dynamic exercise modalities can be used to derive the instantaneous local O_2 consumption in response to imposed

intensity.[181] The regional blood flow during exercise measured by NIRS is validated as well by comparing it to the ^{133}xenon washout technique.[182] Also, recovery of the NIRS signal during the cuff-induced hyperemia can be interpreted as microvascular reactivity, showing a good correlation (r = 0.79-0.98) with conduit artery microvascular parameter (reactive hyperemic blood flow).[183] Similarly, Alvares et al.[184] demonstrated a strong relationship between the tHb signal by NIRS and blood flow measured by Doppler ultrasound during exercise-induced hyperemia.

NIRS in Peripheral Arterial Disease

Accounting for NIRS' non-invasive and cost-effective nature, studies have investigated the employment of NIRS in clinical conditions associated with microvascular dysfunction such as muscle myopathy, heart failure and PAD.[185] In particular, attempts have been made to use NIRS to diagnose PAD. For example, using DUS as the referent for detecting stenosis in lower extremity arteries, the area under the curve (AUC) of O_2Hb, HHb, and differential hemoglobin (O_2Hb-HHb) by NIRS on gastrocnemius with treadmill walking displayed good sensitivity (71-88%) and specificity (92-95%) in identifying PAD in a diseased limb of individuals without CKD.[186] Moreover, the time from cessation of exercise to baseline O_2Hb values (i.e., recovery) has a high correlation and specificity of lower body claudication compared to ABI.[187,188] Similarly, the rate of deoxygenation (slope of HHb curve) during exercise was significantly faster in individuals with PAD with a slower reoxygenation rate (slope of O_2Hb curve) during recovery.[189,190]

Oxygen utilization capacity of the skeletal muscle can also be measured by looking at the recovery rate of tissue oxygenation using NIRS following a period of ischemia. In vivo

mitochondrial oxidative capacity in the skeletal muscle was compared to the recovery rate of the NIRS signal and showed positive association in patients with PAD.[191]

NIRS in Chronic Kidney Disease Population

Currently, only a few studies have examined the microvascular function in peripheral tissues in patients with ESKD using NIRS, as noted in the recent review.[155] Wilkinson et al.[192] demonstrated that the quicker recovery of NIRS parameters (oxygen saturation index) post-exercise is associated with higher exercise capacity in non-dialysis stage 2-3 CKD patients. Miyazawa et al.[193] showed that the gastrocnemius' regional oxygen saturation is lower in individuals receiving HD compared to the healthy controls with an association with serum concentration levels. De Blasi et al.[194] examined the calf muscle using NIRS and found a significant decrease in microvascular compliance during HD sessions in individuals with ESKD, regardless of similar predialysis values as compared to the healthy controls. Combined, the diagnostic ability of NIRS, specifically on peripheral microvascular dysfunction in this clinical population, has not been established.

Feasibility of NIRS

The feasibility of using NIRS in clinical settings is limited by several factors. Despite being non-invasive, NIRS faces challenges in distinguishing the chromophore signal of hemoglobin from that of muscle myoglobin or cytochrome oxidase, due to the similar near-spectrum of light being investigated (700-1000 nm).[195] While the contribution of each chromophore to the NIRS signal has been estimated[196], studies have shown that the relative contribution of myoglobin can vary depending on factors such as exercise[197], blood volume[198], and oxygen levels.[199] While great hemodynamic stress is imposed on the patients receiving

maintenance HD 3-4 times a week[200], the reliability of NIRS parameters at inter- and intra-HD sessions remains undetermined. In addition, the estimation of optical differential path length factors in the skeletal tissue, which is heterogeneous across individuals and regions of interest, is a crucial but inherent challenge of the continuous-wave NIRS technique. The thickness of adipose tissue at the measurement site can also affect the scattering properties and lead to changes in the actual differential pathlength factor.[201]

A physiological calibration process[185] is required in order to compare the NIRS parameters acquired via continuous-wave technique between individuals with different tissue properties or clinical conditions. This can be achieved through complete ischemic occlusion induced by a pneumatic cuff, which involves applying pressure above one's arterial pressure, typically 50mmHg higher than the systolic blood pressure, for 5 minutes.[202] However, this technique can be limited by the acceptability of participants, especially those with medial arterial calcifications, who may require substantially higher cuff inflation pressure to induce a proper occlusion in the limb.

The arterial occlusion for brief periods of time (3 to 5 minutes) is considered to be feasible as it is used for FMD assessment in different clinical populations. Although the majority of studies that utilized the arterial occlusion method in individuals with ESKD did not report any adverse events[203-206], it is worth noting that these studies induced the ischemic condition in the forearm. Therefore, the safety concerns regarding the use of arterial occlusion in the lower limbs have not been fully addressed, given that most vascular lesions associated with PAD development occur in the lower extremities.[207]

The feasibility of the NIRS technique in the ESKD population is constrained by multiple factors. One of these is the undetermined reliability of NIRS parameters obtained during or

between HD sessions, which contributes to a limited understanding and, therefore, to the technique's limited feasibility. Additionally, the physiological calibration process that involves arterial occlusion may not be well-tolerated by individuals with ESKD and could potentially lead to adverse events, particularly with decreased levels of wound healing in peripheral tissues.

2.4 Summary and Study Rationale

In conclusion, current clinical practice for the management of PAD is limited in patients with CKD or ESKD. The most recent guideline by AHA/ACC[107] has not yet incorporated CKD as a risk factor despite the amplified mortality and CV events.[83-86] The guidelines lack clarity and do not provide a recommendation for screening PAD in the CKD and ESKD population despite the clear limitations of clinical tests used for diagnosing PAD: low sensitivity/specificity (ABI, TBI), procedural risk and cost (MRA, CTA), and low accessibility due to the requirement of highly trained professionals (DUS).[131] Other potential alternative diagnostic tools require technical expertise (VTI) and are limited to static assessment (LDF), or have yet to be assessed for diagnostic potential in the ESKD population (NIRS). Since KDIGO reported underdiagnoses of PAD as an issue, developing a reliable tool that can detect subclinical peripheral vascular dysfunction or injury in the ESKD population would be beneficial.[131]

NIRS, with its demonstrated sensitivity in detecting changes in microvascular hemodynamics and its non-invasive nature allowing for dynamic measurement (during exercise or post-occlusive hyperemia), is a potential tool for diagnosing PAD in this high-risk population. However, the existing evidence regarding NIRS' reliability in individuals receiving dialysis is limited, and its feasibility in this context remains largely unknown. Obtaining preliminary data is crucial to conduct future studies that examine NIRS' ability to diagnose

subclinical manifestations of PAD and detect microvascular dysfunction or injury in patients with ESKD.

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Chapter III: Feasibility of Utilizing Near-Infrared Spectroscopy and Peripheral Arterial Tonometry in Lower-Limbs of Patients with End-Stage Kidney Disease

3.1 Introduction

Chronic kidney disease (CKD) is defined as a disease exhibiting markers of kidney damage (proteinuria) or when the estimated glomerular filtration rate (eGFR) is reduced under 60ml/min per 1.73m^2 for over 90 days.[1] In an individual with CKD, the eGFR can progressively decline due to irreversible characteristics of the disease. Once the eGFR falls less than 15ml/min per 1.73m^2, it is defined as end-stage kidney disease (ESKD).[2] Of those with progressive CKD, only 5% will reach ESKD, primarily due to the competing risk of cardiovascular mortality.[3] An individual with ESKD requires kidney transplantation or dialysis modalities to replace the failed kidney function in order to survive.[4] According to the Canadian Organ Replacement Register[5], the incidence of ESKD is ~200 new patients per million per year with approximately 24,000 ESKD people in Canada requiring approximately 12 hours of in-center hemodialysis every week.

ESKD is associated with a high risk of cardiovascular morbidity and mortality due to heightened inflammation, vascular calcification, oxidative stress, and the dialysis treatment.[6] In individuals with ESKD, the risk of cardiovascular death is 4-20 times higher than in individuals with normal kidney function.[7,8] Peripheral arterial disease (PAD) is one of the most common cardiovascular complications affecting 25-46% of the population with CKD.[9] In individuals with dialysis-dependent ESKD with diagnosis of PAD, the event rate of non-traumatic lower limb amputation and ulceration is 74.9 per 1,000 patient-year, with corresponding adjusted hazard ratio of 10.36 (95% CI, 8.83-12.16) compared to individuals with normal GFR without PAD.[10] PAD is independently associated with higher mortality among people with CKD, and the magnitude of risk increases with CKD stage.[11]

The underdiagnoses and undertreatment of PAD in the population with ESKD are recognized as issues despite the deleterious clinical outcomes.[12,13] First, the disease

manifestations of PAD are often asymptomatic, such that only less than 15% of individuals with PAD have symptoms of extremity pain during exertion, which is referred as a typical claudication.[14,15] The first line of recommended screening tools, ankle-brachial index (ABI), has good sensitivity (83-99%)[16] in diagnosing PAD. However, while medial arterial calcification is a common complication in populations with ESKD[17,18], the ABI values are often falsely elevated and decrease its sensitivity (49%)[19]. diagnosing PAD with an increased false-negative rate (~30%).[14,20] As a result, the guidelines by the Trans-Atlantic Inter-Society Consensus[21] for PAD management recommends using the toe-brachial index (TBI), which is relatively free from medial arterial calcification for those individuals with elevated ABI. However, the sensitivity of TBI is questionable when used in individuals with CKD (45%) and individuals receiving HD (45.2%).[22,23]

Diagnostic imaging modalities recommended by the AHA/ACC guidelines for PAD diagnosis, such as computed tomography angiography or magnetic resonance angiography imaging, lack feasibility in the clinical setting due to potential contraindications of the contrast-based agent in the individuals with ESKD and the high cost requiring trained professional and expensive equipment.[24,25] Moreover, the risk of major lower limb complications, such as amputation in individuals with ESKD, is still high even after a successful surgical intervention.[26] Querfeld et al.[27] pointed out that the current screening of diagnostic tools used for PAD are focused on macrovasculature (≥300μm), and are inadequate to detect and treat microvascular dysfunction or injury. As Beckman et al.[28] demonstrated that microvascular disease alone increases the risk of amputation by 3.7-fold without a diagnosis of PAD, it is suggested that microvascular dysfunction is overlooked in the current clinical treatment, and contributes to the increased risk of adverse outcomes for individuals with ESKD.

Compared to the current diagnostic tools, continuous-wave near infrared spectroscopy (NIRS) is a cost-effective, operator-independent non-invasive tool to examine microvascular function that demonstrates potential in diagnosing PAD.[29] Previous studies showed NIRS' sensitivity in detecting changes in microvascular hemodynamics during dynamic measurement (exercise/post occlusive hyperemia).[29-32] Despite the aforementioned need for an alternative tool to examine the microvascular function in the population with ESKD, the existing evidence regarding NIRS' diagnostic accuracy is limited.[33]

The primary goal of this study was to explore the feasibility of using NIRS and PAT-based vascular function tests in the lower limbs for detecting microvascular dysfunction in individuals with dialysis-dependent ESKD. The preliminary data gathered in this process will be utilized to estimate the sample size for subsequent studies that focus on the diagnostic accuracy of NIRS and PAT.

3.2 Purpose

The purpose of this study is to investigate the feasibility of utilizing NIRS/PAT-based vascular function tests on individuals with dialysis-dependent ESKD.

3.3 Hypothesis

We hypothesize that 1) the selected non-invasive tests of microvascular function (NIRS and PAT) will be feasible to obtain and well-tolerated by the individuals with dialysis-dependent ESKD, as measured by *a priori* criteria. 2) The NIRS and PAT measured microvascular parameters will correlate ($r > 0.7$) with the referent test (VTI), 3) NIRS and PAT will differ significantly between individuals in the HD and control group, 4) The NIRS and PAT measured parameters will have good test-retest reliability (ICC >0.7) in the HD group. 5) Individuals in the

HD group with abnormal ABI (<0.90, or ≥1.4) and/or TBI (<0.70) will show significantly slower post-occlusive oxyhemoglobin recovery as measured by NIRS, and lower reactive hyperemia index by PAT compared to the control group. 6) For individuals in the HD group with abnormal ABI (<0.9, or ≥1.4) and/or TBI (<0.70), the vascular parameters will correlate (r>0.7) with the physical activity level (step count per day)

3.4 Methods

3.4.1 Study Design

In this single-center study, we used a cross-sectional design to examine the feasibility and acceptability of utilizing non-invasive vascular screening tools (NIRS and PAT) in the lower limbs of individuals with dialysis-dependent ESKD. The feasibility and acceptability of different vascular tests were assessed based on the *a priori* criteria on measurement quality and patient tolerability. As a secondary aim, we explored relationships between the obtained microvascular measures as well as the macro- and micro-vascular parameters. Individuals with CKD and dialysis-dependent ESKD were invited back for a second visit within 14 days to evaluate the test-retest reliability of the NIRS parameters, which is currently unknown. This study was approved by the University of Alberta Health Research Ethics Board (Pro00115743).

3.4.2 Setting and Participants

Recruitment and Eligibility

Individuals with CKD or dialysis-dependent ESKD were recruited through the outpatient setting, which included a renal insufficiency clinic at the University of Alberta site and HD units in the Edmonton zone. Participants were recruited via passive strategy (i.e., posters in the clinics

and units) or the interested patients were identified by the clinical team, and then recruited by study coordinators. We first recruited from the HD units and therefore no individuals with CKD were enrolled during the recruitment period for this thesis. Healthy controls were recruited via posters distributed within the University of Alberta campus. Individuals recruited as healthy controls were screened via an interview by the study coordinator based on our inclusion criteria (Appendix A). The healthy controls were free of cardiovascular disease, diabetes, or kidney disease based on self-report. In the HD group, individuals with acute kidney injury or critical limb ischemia were excluded from the study. All participants provided written, informed consent. We analyzed the results of a total of twenty-one healthy controls and fourteen individuals with dialysis-dependent ESKD for this ongoing study.

3.4.3 Baseline Data Collection

Demographics and clinical characteristics

Basic demographic data was collected during the lab visits. The participants were asked of their age, biological sex, and gender. The clinical information of each individual in the HD group was obtained from ConnectCare by a member of the study team. All collected data were entered into Research Electronic Data Capture (REDcap)[34,35] hosted at the University of Alberta, and each participant was given an arbitrary study number. A separate file that contains identifiable personal data linking participants to their study number was password protected and saved on a secure University of Alberta network only accessible to the research coordinator.

Functional status survey

All participants received a San Diego Claudication Questionnaire[36] and Walking Impairment Questionnaire[37] to evaluate their walking impairment or any symptoms of

claudication. These questionnaires were emailed to each individual via RedCap survey function[34,35] prior to the first visit. For those individuals who did not have access to the provided link, the questionnaires were completed during the resting period of the lab visits. Individuals were categorized based on their answers on the San Diego Claudication Questionnaire; “no pain”, “pain at rest”, “non-calf pain”, “classic claudication” or “atypical calf pain”.[36] For the Walking Impairment Questionnaire, each individual was scored in three categories: walking velocity, walking distance, and stair climbing. The degree of difficulty in each category was obtained by ranking on zero to four Likert scale, and converted to the percent score by dividing with the maximum possible score.[38]

Physical activity monitoring

The participants' levels of physical activity were evaluated by determining their average daily step count using a previously validated activity monitor (Fitbit Flex 2, Fitbit Inc., San Francisco, CA, USA).[39] Each participant received a Fitbit device, with instructions to wear the wristband tracker for at least seven consecutive days. They were only to remove it when showering, bathing, or sleeping. For those in the HD group, the Fitbit device was given at their first visit and was subsequently collected from them during their second visit. For the control group, the Fitbit device was handed over at least a week prior to their initial visit and was collected when they came in for their laboratory visit. Participants did not have access to any information about their physical activity (such as step count or heart rate) during the monitoring period.

The level of physical activity was quantified by calculating the average number of steps taken each day during seven or more consecutive days. The measurement length of five or more consecutive days is adequate to achieve reliable estimate of each individual’s physical activity level.[40,41]

3.4.4 Procedures and Measurements

As per the latest recommendations for vascular responsiveness test (FMD)[42], every participant was instructed to follow pre-test instructions including withholding any food consumptions for six hours, and refraining from any coffee, tea, alcohol, smoking and vasoactive drugs for twelve hours prior to the visit. All visits were conducted in a temperature-controlled and dimly lit environment (0A8.16, ABACUS, Mazankowski Alberta Heart Institute, University of Alberta Hospital) and conducted by the same tester (EB).

Upon first arriving at the lab, each participant's height and weight were recorded followed by ten minutes of supine rest to achieve hemodynamic stability prior to the measurements. Each lab visit appointment for the individuals on HD was scheduled on standardized non-HD days at a similar time of the day for physiological stability. The second visit was scheduled ≥48hours and within fourteen days from the first visit. The same procedures were repeated in the second visit.

Ankle-brachial and Toe-brachial Index

The ankle-brachial index (ABI) was calculated as a ratio of systolic blood pressure between the ankle and brachial artery.[43] Detailed calculation is described under Appendix B. An ABI value between 0.90 and 1.40 was considered normal, and a value <0.90 or ≥1.40 was considered abnormal.[14,24] The toe-brachial index (TBI) was calculated as a ratio of systolic blood pressure between the great toe and brachial artery.[43] Both the ABI and TBI were measured according to the standard recommended by the AHA[24] using the Smartdop XT peripheral vascular diagnostic system from KOVEN Technology Inc. (St. Louis, MO, USA) after the participant rested for 10 minutes in a supine position.

To measure the brachial artery pressure of the upper extremities, a pneumatic cuff was placed on the upper arm above the location of the Doppler probe. If there were any complications such as a fistula, graft, or vascular access in one arm, measurements were taken from the other arm. Subsequently, systolic blood pressure in the toe was obtained. Depending on the morphology of the participant, a toe cuff of either 1.9cm or 2.5cm width was used. The cuff was wrapped around the proximal phalanx of the participant's big toe. In addition, a volume photoplethysmography sensor was secured on the underside of the participant's big toe, distal to the location of the cuff. The Smartdop XT system was then used to automatically measure toe systolic pressures.

The Smartdop XT system automatically measured toe systolic pressures. After obtaining toe pressures, the posterior tibial and dorsalis pedis arteries in each ankle were assessed. The cuff was placed 2cm proximal to the top of the medial malleolus, and its width was chosen to cover at least 40% of the calf circumference.[43] To perform the measurement, the cuff was inflated to 20mmHg above the point where the flow signal disappeared, and then progressively deflated, with the maximum inflation pressure capped at 280mmHg. Each site was measured twice for blood pressure. If the two measurements differed by more than 5mmHg, a third measurement was taken.

For the calculation of the Ankle-Brachial Index (ABI), the higher systolic blood pressure recorded from either arm was used as the denominator.[43] Then, the average pressures of the posterior tibial and dorsalis pedis arteries from each side were used as the numerator. In the cases of TBI ≤ 0.70, ABI < 0.90 or ≥ 1.40, the attending physician was notified.

Measurement 1 - Reactive Hyperemia on Brachial Artery

Following the ABI/TBI measurements, the participant remained in the supine position. The side of the upper limb that showed lower ABI/TBI was assessed with pulse-wave Doppler ultrasound (GE, Vivid-7, Horten, Norway). If the participant had a maturing fistula or graft on the upper limb, the other side was used. The participant's endothelial function was assessed at the brachial artery utilizing cuff-induced reactive hyperemia FMD as per previously established guidelines.[44] For brachial artery FMD (BA-FMD), a manually inflated pneumatic cuff was placed on the forearm distal to the antecubital fossa. The transducer was stabilized using a stereotactic probe holder while maintaining the insonation angle of 60̊ or less with the sample volume adjusted to the vessel diameter. Once a clear vascular boundary was found, the ultrasound image was recorded continuously via commercially available software (FMD studio, version 4.5, Quipu, Pisa, Italy). The instant changes in arterial diameter in millimeters (mm) and flow velocity (cm/sec) were recorded to a fraction of a millisecond (ms), and automatically converted to the average value per second. The diameter and flow velocity were recorded continuously throughout the baseline (one minute prior to the cuff occlusion), cuff occlusion (five minutes of suprasystolic pressure; 50mmHg + highest systolic blood pressure), and during the reactive hyperemia (five minutes after the cuff deflation).[42] The detailed calculations of FMD parameters is described in Appendix C.

Pulse amplitude tonometry (PAT) is considered another way to measure endothelial function.[45] Each participant's digital arterial function was assessed using Endo-PAT 2000 (Itamar Medical Ltd, Caesarea, Israel) following the previously published detailed procedure.[46] PAT was assessed in each participant at the same time as their BA-FMD measurements. Two probes were used to cover the distal phalanx of either index or middle finger on each hand. The previously measured diastolic pressure from the upper limb was entered into the Endo-PAT

program, allowing the probes to be inflated to the sub-diastolic pressure to prevent venous pooling and minimize the arterial wall motion.[47] The changes in pulse amplitude were recorded continuously; prior to the cuff inflation or baseline (5min), arterial occlusion (5min), and reactive hyperemia (5min). The collected data were automatically analyzed by the built-in program (Endo-PAT version 3.4.4, Itamar Medical Ltd, Caesarea, Israel).

Measurement 2 – Reactive Hyperemia on Popliteal Artery

Following the BA-FMD, the participant was asked to switch to the lateral decubitus position with the legs slightly elevated and supported by inflatable pillows. The lower limb unilateral to the assessed brachial artery was examined. If the unilateral side of the lower limb was unavailable, the contralateral limb was examined instead. A rapid inflation cuff (E-20, Hokanson, Bellevue, WA, USA) was placed on the belly of the anterior tibialis about 5cm distal to the popliteal fossa. The ultrasound transducer was positioned perpendicularly to the artery being imaged, proximal to the popliteal fossa. The changes in arterial diameter and shear rate stimulus were recorded following the same guideline used for BA-FMD.44

Near-infrared spectroscopy (NIRS) was utilized during the PA-FMD procedure described above. A continuous-wave NIRS device (Artinis Oxymon Mk III Artinis Medical Systems, Elst, The Netherlands) was used to obtain the level of Oxygenation state of the tissue; the changes in oxygenated (O_2Hb), deoxygenated (HHb), or total concentration of hemoglobin (tHb) and myoglobin were collected at 10Hz. The NIRS signals were set to an arbitrary value of zero as a baseline signal (30 seconds prior to the cuff occlusion). A moving average Gaussian filter at a width of 1 second to calculate a 1 second average was applied to NIRS signals prior to analysis as described in the NIRS literature.[48,49] A single channel using one light emitter and one receiver optode was placed horizontally on the muscle belly of the tibialis anterior distal to the ultrasound

transducer and pneumatic cuff. The interoptode distance was maintained at 50mm and the maximum penetration depth of the light at approximately 25mm with wavelengths of 761 and 846 nm. The NIRS device was set with a constant differential path length factor of 6.26.[50] The participant's adipose tissue thickness under the probe was measured using the Doppler ultrasound and recorded in millimeters following the PA-FMD measurement. The NIRS measurement was done during the reactive hyperemia protocol (PA-FMD). The resting baseline value was recorded for one minute followed by five minutes of suprasystolic cuff occlusion. Once the cuff was deflated, NIRS signals were recorded continuously for five minutes. The detailed analysis of NIRS signals is in Appendix D and E.

3.4.5 Data Collection and Analysis

A Priori Criteria for Feasibility Outcomes

To evaluate the feasibility of different vascular tests, we utilized four different categories: acceptability, technical adherence, interpretability, and incidence of adverse events. We established an arbitrary threshold of 10% for each criterion as a benchmark for determining feasibility. Acceptability was assessed based on participant comfort during the tests. Any test that had to be terminated due to discomfort experienced by the participant was classified as "unacceptable". The popliteal FMD and NIRS were performed during the same ischemic challenge therefore termination was counted toward both tests. The technical adherence component involved successful execution of the test without encountering technical difficulties such as inability to detect signal, machine malfunction, or calibration errors. Tests halted due to such complications were considered "technically non-adherent". To calculate the proportion of "unacceptable" and "technically non-adherent" tests, we divided the number of participants who encountered each of these issues by the total number of participants in each group (HD and

controls). Interpretability referred to completed tests that had any parameter classified as unreliable due to factors such as unstable images or signals, or absence of data, thus considered "uninterpretable". The number of uninterpretable tests was derived from the total number of participants in each group who completed each test without termination. Lastly, adverse events were defined as any potential test-induced unfavorable symptoms or, signs, such as pain, bruising, or functional impairment. Any abnormalities in the tested limbs occurring within a 48-hour period post-testing were considered as test-related adverse events.

3.4.6 Statistical Analysis

Statistical analysis was completed utilizing the R software.[51] The independent t-test was employed to identify any significant differences between the mean values of each group. The test-retest reliability of each vascular parameter obtained via NIRS and PAT through two visits in the HD group was analyzed using a variety of methods. These included the calculation of the coefficient of variation (CV), the intraclass correlation coefficient (ICC) using a two-way mixed-effects single-measurement model for absolute agreement, the standard error of measurement, the minimal detectable change, and Bland-Altman plots.[52] In Bland-Altman plots, the degree of difference between the repeated measurements obtained during the first and second visits was plotted against their mean using a scatter plot. The variance of these differences was used to calculate the 95% confidence interval as the limits of agreement of each parameter. While the bias within the confidence intervals was regarded as an agreement, defining *a priori* maximum acceptable differences in limits of agreement was unavailable due to the heterogeneity of NIRS research.

We utilized the Pearson correlation coefficient and linear regression analysis between variables obtained from different vascular function tests to determine the degree of association

between macro- and micro-vascular parameters. Data are expressed as the mean ± SD unless otherwise indicated. A p-value of less than 0.05 was considered statistically significant.

3.5 Results

Participants

The characteristics of all participants are shown in Table 1. A total of fourteen individuals with HD-dependent ESKD and twenty-one controls participated and were included in the analysis. Among the individuals in the HD group, thirteen completed both visits. The HD group was predominantly males (n=14; 12 males, 2 females) with an average age of 58.4 ± 11.7 years. The control group contained eight males and thirteen females with an average age of 31.2 ± 11.1 years. The HD group exhibited significantly higher resting systolic blood pressure (147 ± 34 vs. 111 ± 9 mmHg, $p<0.01$). The clinical characteristics of individuals in the HD group are presented in Table 2. Among the individuals on HD, ten had diabetes mellitus, two had coronary artery disease, and six had dyslipidemia. Diabetic nephropathy was the primary cause of ESKD in 71% (n=10), while the majority of the HD group (86%) used antihypertensive medication. For vascular access, all individuals of the HD group either had a fistula, representing 43% (n=6), or a central venous catheter, accounting for 57% (n=8).

Feasibility Outcomes

To evaluate the feasibility and acceptability of PAT and NIRS-based vascular tests in patients with dialysis-dependent ESKD, four feasibility outcomes were evaluated based on *a priori* criteria. The assessment of these feasibility outcomes for each vascular test in the HD group and the control group is shown in Table 3 and Table 4, respectively.

Acceptability

Four individuals in the HD group (n=4, 28.5%) and none in control group (n=0, 0%) were unable to tolerate NIRS-based vascular function test and PA-FMD test due to discomfort. Two of those individuals only manifested discomfort in the second lab visit. In the NIRS-based vascular function test and PA-FMD test, discomfort experienced by the four individuals on HD was a result of arterial occlusion in the calf (n=4, 28.5%). In comparison to the 10 individuals in the HD group who tolerated the ischemic challenge, these four individuals exhibited significantly higher baseline ankle systolic blood pressure (223 ± 22 vs. 155 ± 35 mmHg, $p<0.05$). There were no significant differences observed in ABI (1.21 ± 0.20 vs. 1.15 ± 0.15, p=60) and TBI (0.69 ± 0.42 vs. 0.89 ± 0.10, p=43) between the individuals who terminated tests due to discomfort from cuff inflation vs. those who did not (Table 5). None of the tests were terminated due to participant discomfort from the body position, duration of tests, or any other sources.

Technical Quality

Technical issues were encountered during the collection of ABI and TBI in two individuals (n = 2, 14%) from the HD group and two individuals (n = 2, 9.5%) from the control group. These issues were due to unstable Doppler pulse signals in the ankle or toe arteries.

Interpretability

All fourteen individuals in the HD group completed the arterial occlusion test in the upper limb. Eight out of fourteen individuals had at least one uninterpretable PAT (55%). Of the total 27 PAT tests conducted, ten produced invalid signals (37%) and three returned noisy signals (11%). A subgroup analysis of those individuals with uninterpretable PAT results is

presented in Table 6. One participant in the HD group had uninterpretable BA-FMD results (n=1, 7%) due to uninterpretable VTI and arterial diameter data.

Eleven individuals in the HD group completed at least one lower limb arterial occlusion test. Among these eleven individuals, eight had uninterpretable PA-FMD tests (n=8, 72%), and two had uninterpretable NIRS data (n=2, 18%). Out of 21 arterial occlusion tests done in the lower limb, satisfactory data were obtained in 55% of PA-FMD tests, and 90% of NIRS tests. Seven of PA-FMD tests had uninterpretable VTI (30%), four had unstable diameter (19%), and two had incomplete arterial occlusion making NIRS uninterpretable (9%).

In the control group, which comprised 21 individuals, all participants successfully completed PAT, NIRS, BA-, and PA-FMD tests. However, certain issues were faced in the interpretation of the test results. Out of the total PAT tests conducted, eight were uninterpretable, making up 38% of the tests, due to invalid signals (n=6) or poor signal quality (n=2). As for the BA-FMD tests, 95% (20 out of 21 tests) yielded successful results, with one test deemed uninterpretable due to unreliable BA-VTI and diameter readings. There were nine instances of unreliable PA-FMD tests (43%), attributed to uninterpretable VTI (n=7) and diameter (n=2). In contrast, all the NIRS tests (100%) conducted in the control group yielded successful results with no interpretability issues.

Adverse Events

In the HD group, one out of fourteen individuals (7%) manifested pain in the occluded upper and lower limbs. The participant described it as “minor discomfort” and stated that it disappeared after taking over-the-counter analgesic within the day. Similarly, one individual in

the control group (1/21, 5%) reported experiencing mild leg strain, which they subjectively rated as a 2-3 out of 10 on the pain scale.

Correlation between NIRS/PAT and VTI

The correlation analysis of NIRS and PAT parameters in relation to VTI is separately displayed for the HD group (Table 9), the control group (Table 10), and both groups combined (Table 11). In the HD group, there were no correlations observed between NIRS and either FMD or PAT parameters, except for a correlation between $mVO_{2\%}$ and normalized $FMD_{\%}$ to shear rate ($r=0.70$, $p=0.02$). As for the microvascular parameter (BA-VTI), $mVO_{2\%}$ showed a correlation trend ($r=-0.43$, $p=0.21$). When the HD and control groups were combined, $mVO_{2\%}$ had a moderate negative correlation with BA-VTI ($r=-0.54$, $p<0.01$), and $T_{baseline}$ showed a weak negative correlation with BA-VTI ($r=-0.37$, $p=0.04$). In PAT parameters, the augmentation index normalized to heart rate of 75 (AI@75) showed notable correlation with the BA-VTI ($r=-0.66$, $p<0.01$). The correlation between RHI assessed by PAT and BA-VTI was negligible ($r=-0.06$, $p=0.81$).

Test-retest repeatability of NIRS/PAT

The results of the test-retest reliability analysis in the HD group are presented in Table 7. Among the NIRS parameters, $mVO2_{\%}$ demonstrated excellent reliability with an intraclass correlation coefficient (ICC) of 0.96 (95% CI: 0.81-0.99) and a coefficient of variation (CV) of 3.9%. The other recovery parameters of NIRS exhibited moderate to good reliability, with ICC values ranging from 0.50 to 0.90, and CV ranging from 16.5 to 22.8%. The minimal detectable change in temporal parameters ($T_{baseline}$ and $T_{50\%}$) were 9.6 and 9.8 seconds, respectively. In five participants in the HD group who completed two visits with successful PAT results, RHI showed

poor reliability (ICC = 0.40) while the AI@75 showed excellent reliability (ICC = 0.95). The CV of RHI was 11.4% with minimal detectable change of 1.21. On the other hand, AI@75 had 32.1% of CV and minimal detectable change of 4.99 (a.u).

The Bland-Altman plots for NIRS parameters are shown in Figure 2. The calculated mean difference and limits of agreement in $mVO_{2\%}$, $R_{recovery}$, and $R_{baseline}$ were found to be: 0.004 (LoA; -0.0350 ~ 0.0359), 0.6 (-2.9 ~ 1.8), and -0.6 (-1.5 ~ 0.3), respectively. A bias of 0.1 seconds was observed in the case of $T_{50\%}$ between two visits, while $T_{baseline}$ demonstrated a substantial bias of 6.3 seconds. In the linear regression analysis, only $T_{baseline}$ indicated that individuals with longer time taken for recovery showed more variation ($r=0.52$, $p=0.009$). Figure 3 illustrates the Bland-Altman plots of PAT parameters. The bias of RHI was 0.11 (a.u) while AI@75 was 4.35 (a.u).

Comparison of Ankle- and toe-brachial index between groups

The results of the clinical tests (ABI and TBI) are reported in Table 5. The ABI value was significantly higher in the HD group compared to the control group (1.16 ± 0.16 vs. 1.00 ± 0.07, $p<0.01$) while the TBI value was significantly lower compared to the healthy individuals (0.83 ± 0.24 vs. 1.08 ± 0.13, $p<0.05$). Only two individuals in the HD group had abnormal TBI values (less than 0.70), while only one had an abnormal ABI value (higher than 1.40).

Comparison of NIRS/PAT between groups

Table 8 presents the comparison of NIRS/PAT parameters between the HD and control groups. The thickness of adipose tissue in the tibialis anterior muscle, where the probe was placed, showed no significant difference between the groups (3.54 ± 0.85 vs. 3.69 ± 0.69mm, $p=0.63$). The HD group had significantly higher muscle oxygen consumption ($mVO_{2\%}$, 0.27 ±

0.05 vs. 0.20 ± 0.03 p<0.01), and showed a trend towards slower recovery to baseline ($T_{baseline}$, 23.6 ± 10.9 vs. 16.1 ± 5.6, p=0.06) compared to the control group. Moreover, the HD group had significantly smaller hyperemic response as represented by the area under the curve for 2 minutes (AUC_{2min}, 3153 ± 1684 vs. 5155 ± 2406 a.u, p<0.01). The half time recovery ($T_{50\%}$) and the recovery slopes ($R_{baseline}$, and $R_{recovery}$) were not different between groups.

The RHI in the HD group was not significantly different from the control group (1.90 ± 0.39 vs. 1.76 ± 0.35 a.u, p=0.40). However, the normalized augmentation index was significantly higher in the HD group (17.66 ± 25.12 vs. -13.18 ± 10.76 a.u, p<0.05).

Sub-group analysis of individuals with abnormal ABI/TBI

Only two individuals manifested abnormal ABI/TBI based on the predetermined criteria, thereby constraining the statistical analysis. Therefore, the comprehensive validation of our initial hypothesis was unavailable. However, we explored the correlations between the vascular parameters and physical activity levels in the combined group (Figure 4-5). Among the NIRS parameters, $mVO_{2\%}$ (r=-0.57, p<0.01, panel A), $T_{baseline}$ (r=-0.43, p=0.03, panel C) and AUC_{2min} (r=0.63, p<0.01, panel F) had moderate correlation with the physical activity level as evaluated by daily step count, while the slopes during recovery ($R_{baseline}$ and $R_{recovery}$) had no correlations. In PAT-measured parameters, AI@75 showed a trend towards moderate correlation (r=-0.43, p=0.07, Figure 5, panel B).

Comparison of BA- and PA-FMD between groups

Table 12 displays the results of BA- and PA-FMD between the groups. Individuals in the HD group had significantly larger brachial diameters compared to the control group at both baseline (4.64 ± 0.69mm vs. 3.53 ± 0.62mm, p<0.01) and at the peak dilation (4.79 ± 0.69 vs.

3.93 ± 0.62mm, p<0.01). However, the HD group had significantly lower absolute dilation, percentage dilation to baseline (BA-FMD%), VTI, baseline- and peak average velocity in the BA-FMD test compared to the control group (p<0.01).

There was no difference in the popliteal arterial diameter at both baseline and the peak between groups. The PA-FMD% were not different between the groups (5.19 ± 1.94 vs. 6.51 ± 2.56%, p=0.13). On the other hand, individuals in the HD group had significantly lower shear rate to the peak dilation (10133.8 ± 3748.2 vs. 17711.8 ± 9080.7 a.u, p<0.01) and lower VTI (48.8 ± 9.9 vs. 74.3 ± 14.5cm, p<0.01) compared to the control group.

3.6 Discussion

The current study is the first to investigate the feasibility of utilizing NIRS- and PAT-based vascular tests in the lower limbs of patients with ESKD, with the aim of detecting subclinical vascular dysfunction. We evaluated each vascular test based on four feasibility outcomes: acceptability, technical quality, interpretability, and incidence of adverse events. Initially, our results revealed that a significant portion of the PA-FMD tests were not interpretable due to inconsistent diameter imaging or the inability to capture VTI. This was largely attributed to sudden movements made by the participants following the inflation or deflation of the pneumatic cuff, and/or the cuff itself disrupting image stability. In contrast, NIRS-based testing was capable of capturing stable signals despite these movement-related challenges, indicating that NIRS testing is less influenced by movement artifacts. Second, we encountered issues regarding the acceptability of arterial occlusion in the calf, particularly within the HD group. For some individuals in the HD group, especially those with high ankle systolic blood pressure, the application of suprasystolic pressure resulted in considerable discomfort to the extent that the test was terminated. Third, the PAT test done on the index fingertip was well

accepted by individuals across both groups. However, the interpretability of these tests in the HD group is questionable. A significant proportion of the tests were deemed uninterpretable due to excessive noise or invalid signals being captured. Lastly, we did not record any major adverse events related to the arterial occlusion applied in the lower limbs. This observation was consistent across both the HD and control groups, demonstrating the safety of arterial occlusion challenges in populations with dialysis-dependent ESKD.

Arterial occlusion in the lower limb

A multitude of studies have focused on the vascular function of individuals with dialysis-dependent ESKD. These studies utilized several different methods such BA-FMD[53-55], laser-doppler flowemtry[56], or PAT[57] on the upper limbs. In contrast, we targeted the lower limb as the region of interest in our research, which is driven by several key reasons. One compelling reason is that the individuals receiving HD often have arteriovenous fistula or graft on the forearm as a type of peripheral vascular access, as a result of surgical intervention to form anastomosis between the vein and artery.[58] The presence of these fistulas or grafts could potentially influence the outcomes of vascular assessments. However, little is known of the influence of these fistulas or grafts on vascular parameters, leading to potential limitations and unreliability in assessing the upper limb vascular function in this clinical population. Given that the use of fistulas or grafts is being widely encouraged in clinical practice[59], this issue is of particular importance. Targeting the lower limbs would allow us to investigate an area unaffected by these modifications.

In addition to avoiding the potential impact of fistulas or grafts, focusing on the lower limbs may offer further advantages. A prior study[60] reported that the atherosclerotic structural remodeling is segmental, suggesting that the changes in vascular function can be localized in individuals with clinical or sub-clinical atherosclerotic occlusive disease. Given that PAD, a

common manifestation of atherosclerotic disease, is mostly found in the lower limbs[61], our choice of the lower limb may be more sensitive in detecting the changes in vascular function. Furthermore, the majority of arterial lesions in lower limb PAD are located above the knee regions.[62] Therefore, examining the lower limbs, particularly areas distal to potentially damaged vascular structures, could increase sensitivity in detecting changes in vascular function compared to the upper limb vasculature.

We also utilized the arterial occlusion method as a part of PA-FMD and NIRS tests in the lower limbs. First, the pneumatic cuff applied at the conduit artery level occludes the blood flow to distal microvasculature. While the microvasculature is dilated during ischemia, the magnitude of reactive hyperemic response captured by FMD or NIRS provides insight on microvascular function.[63] Second, arterial occlusion facilitates the physiological calibration of NIRS. This calibration is essential for allowing comparisons between individuals, particularly when using NIRS in the presence of heterogeneous tissue composition. Finally, when compared to the venous occlusion method, NIRS demonstrated greater reproducibility, albeit in healthy populations.[64]

Discomfort due to cuff inflation

In our study, out of fourteen individuals in the HD group, four reported discomfort resulting from suprasystolic cuff inflation on the calf. During this arterial occlusion, the mechanical stimuli from cuff inflation promotes nociceptive pain via myelinated A-delta fibres and unmyelinated C-fibres.[65] About a quarter of individuals who suffer from diabetic neuropathy are symptomatic where this subgroup do not lose the pain sensations but rather present chronic pain.[66] Ørstavik et al.[67] examined the pathological afferent C-fibres and reported hyperexcitability of this mechano-sensitive fibres, suggesting that those individuals with chronic

painful diabetic neuropathy may be more sensitive to the sensations induced by the cuff inflation. In our study, a detailed subgroup analysis uncovered that those four individuals who reported discomfort during lower limb occlusion had significantly higher ankle systolic blood pressure, with no variation in the ABI, and all four individuals were diagnosed with diabetes mellitus. We did not objectively confirm the presence or type of diabetic neuropathy in our study. However, seeing that the diabetic neuropathy is extremely common in the dialysis-dependent population[68,69], the four individuals in our study may be more sensitive to cuff inflation-induced nociceptive pain compared to those without, further contributing to the reported discomfort.

Uninterpretable data

The NIRS-based vascular function test using arterial occlusion aims to create a closed-circuit system, whereby there are no changes in the tissue hemoglobin (tHb) signal in the area of interest. In our study, two individuals from the HD group presented signals where tHb signals during the arterial occlusion increased. Previous research suggests that an initial increase in hemoglobin signal following cuff inflation might result from blood redistribution within the circulatory system.[70,71] However, in two of participants in the HD group, the tHb signals increased continuously throughout the occlusion period, and dropped immediately following the cuff deflation. The tHb signal during the recovery could not regain the tHb level at the end of occlusion period, suggesting that the cuff inflation created a one-way circulation system, compromising the reliability of both resting mVO_2 and recovery parameters.

The automated computation of pulse amplitude analysis in the PAT test minimized interobserver measurement variability.[72] Yet, a high rate of uninterpretable data was observed in the HD group, with eight out of fourteen individuals presenting such data. In comparison, a larger cohort study involving over 200 participants reported a completion rate of around

90%.[73,74] In the study by Hamburg et al.[74], noisy signal quality accounted for 3% of incomplete data, a finding mirrored in our study with three out of 27 tests (11%) deemed uninterpretable due to noisy signal. It remains unclear whether they included or excluded tests with invalid signals (validity <80%), while we chose to exclude all tests with invalid signals, accounting for 37% of uninterpretable data.

The reason behind the lower PAT signal quality in our study remains uncertain. Intriguingly, individuals with uninterpretable PAT data had significantly lower TBI and near statistically significant lower ABI compared to others in the HD group. Lower TBI may suggest that the pulse to the digital artery (toe or fingers) is diminished in these individuals, potentially causing unstable signals compared to those with stable end capillary pulses. Also, this could be attributed to hand ischemia, a common complication associated with dialysis vascular access creation.[75] Even though we did not examine the upper limb side with vascular access, that side still serves as a control for pulse amplitude, essential for calculating PAT. Finger pressure is directly linked to hand saturation levels. Hand ischemia may affect blood flow at the digital arterial level and alter pulse amplitude.[76]

A significant number of PA-FMD tests in the HD group were not interpretable. This may have been due to the fact that PAD, defined as blood flow obstruction in the arteries, might be present[77], yet we did not have any comparative measurements to determine if any level of arterial stenosis was present in the individuals' lower limbs. In other words, in such cases, arterial narrowing may have interfered with the quality of diameter signals.[78] Moreover, acquiring Doppler flow signals from specific areas within the vessel lumen can be challenging due to arterial constriction.[79] Ultrasound beams are directly attenuated by the adipose tissue, and its

distribution can affect signal quality[80], further exacerbating the challenges associated with utilizing ultrasound-based vascular function tests.

Adverse events

The application of suprasystolic pressure in the limbs specifically in individuals with potentially reduced vascular perfusion presents certain safety considerations.[81] Specifically, cuff inflation can escalate systemic inflammatory responses, impede wound healing[82], risk damage to neuromuscular junctions leading to functional impairment[83], and enhance the chances of thromboembolism.[84] The inflation time of pneumatic cuff for occlusion has been recommended to be minimal to avoid those potential complications.[85] The safe duration for cuff-induced ischemia is currently unknown.[86] However, durations of two hours or less, and brief periods of ischemic challenges (~5 minutes) have not been associated with major adverse events.[87] Our current study lacks certainty on whether our participants were experiencing baseline peripheral tissue ischemia, is which case, an additional 5 minutes of ischemic challenge could exacerbate existing symptoms or cause damages to the distal tissue. However, past research applying arterial occlusion in individuals with PAD reported no adverse event beyond tremor or discomfort leading to the termination of the test.[88,89] Similarly, there was no major adverse events in our study, suggesting that the vascular function test utilizing arterial occlusion is safe even in these select individuals with ESKD.

3.5 Conclusion

Our study demonstrated that the NIRS/PAT-based vascular function test, when combined with arterial occlusion, is safe for individuals with dialysis-dependent ESKD. However, factors like potential vascular calcification or presence of diabetic neuropathy impacted the tolerability

of arterial occlusion for these individuals. The rate of incomplete or uninterpretable tests suggests that the current procedures may not be feasible for the population with ESKD. On a positive note, NIRS/PAT parameters exhibited test-retest reliability, even in the presence of potential arterial structural alterations, variations in individual body morphology, and movement artifacts. Furthermore, our correlation analysis of microvascular parameters (NIRS/PAT/VTI) indicates that measurements like $mVO2_{\%}$, $T_{baseline}$, and AI@75 could serve as markers of an individual's microvascular function. Combined, the findings from this study suggest that NIRS/PAT have potential values in screening PAD in the population with ESKD, though procedural modifications are needed to enhance the feasibility. This study's data will inform sample size calculations for future diagnostic studies with the purpose of utilizing NIRS/PAT in the development of more sensitive and accurate vascular function tests for the population with ESKD.

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Table 1. Characteristics of participants at visit 1

	HD group	Controls	P-value
N	14	21	
Age, years	58.4 ± 11.7	31.2 ± 11.1	<0.01
Male sex, n (%)	11 (79%)	8 (38%)	<0.05
Ethnicity, n (%)			
Indigenous	0 (0%)	0 (0%)	-
Black	2 (14%)	0 (0%)	-
East Asian	0 (0%)	2 (9%)	-
Latino/Latina/Latinx	1 (7%)	3 (14%)	-
Middle Eastern/West Asian	0 (0%)	1 (5%)	-
Polynesian	0 (0%)	0 (0%)	-
South Asian	3 (21%)	6 (28%)	-
Southeast Asian	1 (7%)	2 (9%)	-
White	7 (50%)	5 (24%)	-
Another race	0 (0%)	2 (9%)	-
Height, cm	169.2 ± 5.8	167.3 ± 9	0.47
Weight, kg	75.9 ± 18.3	68.2 ± 13.4	0.19
BMI, kg/m^2	26.3 ± 4.9	24.3 ± 3.7	0.19
Dry Weight, kg	76.7 ± 17.8	-	-
Systolic Blood Pressure, mmHg	147 ± 34	111 ± 9	<0.01
Diastolic Blood Pressure, mmHg	78 ± 15	68 ± 7	<0.05
Mean Arterial Pressure, mmHg	101 ± 20	83 ± 7	<0.01
Smoking history n (%)	7 (50%)	2 (10%)	-
Pack-years	19.4 ± 10.0	1.6 ± 2.0	<0.01
Average steps per day, steps (n)	4090 ± 2384 (n=11)	8489 ± 2748 (n=16)	<0.01
WIQ Score, % (n)	65.5% (n=9)	98.2% (n=20)	<0.05
San Diego Questionnaire, n (%)	N = 9	N= 20	
No Pain	7 (78%)	20 (100%)	-
Pain at rest	2 (22%)	0 (0%)	-
Non Calf IC	0 (0%)	0 (0%)	-
Classic IC	0 (0%)	0 (0%)	-
Atypical Calf IC	0 (0%)	0 (0%)	-

BMI; Body mass index, CKD; Chronic kidney disease, ESKD; End-stage kidney disease, HD; hemodialysis, IC; Intermittent claudication WIQ; Walking impairment questionnaire.

Table 2. Clinical characteristics of individuals in HD group

	HD group
N	14
Etiology of CKD	
Diabetic Nephropathy	10 (71%)
Vascular/Hypertension	5 (36%)
Glomerulonephritis	0 (0%)
Polycystic Kidney Disease	0 (0%)
Interstitial Nephritis	0 (0%)
Hereditary Nephritis	0 (0%)
Unknown	1 (7%)
Others	2 (14%)
Current Medication	
Vasodilatory agent (e.g., cilostazol, pentoxifylline)	3 (21%)
Oral hypoglycemic	2 (14%)
Insulin	6 (43%)
Aspirin	4 (28%)
Statin	9 (64%)
Anticoagulant	6 (43%)
Antihypertensive	12 (86%)
No. of Antihypertensive	1.6 ± 0.7
Days from HD initiation, days	102 ± 55
Medical History, n (%)	
Diabetes Mellitus	10 (71%)
Coronary Artery Disease	2 (14%)
Dyslipidemia	6 (43%)
None of the above	4 (29%)
Vascular Access	14 (100%)
Fistula	6 (43%)
Central Venous Catheter	8 (57%)

HD; hemodialysis. Mean ± SD.

Table 3. Result of Feasibility Assessment in HD group (n=14)

	ABI/TBI	PAT	Brachial FMD	Popliteal FMD	NIRS
Termination due to participant discomfort N (%)	**0/14 (0%)**	**0/14 (0%)**	**0/14 (0%)**	**4/14 (28%)**	**4/14 (28%)**
Discomfort from cuff inflation	0 (0%)	0 (0%)	0 (0%)	4 (28%)	4 (28%)
Duration of test	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Termination due to technical issue n (%)	**2 (14%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
Unable to find stable signal	2 (14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Program Error	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Uninterpretable Data n/N (%)	0/14 (0%)	**8/14 (57%)**	**1/14 (7%)**	**7/11 (63%)**	**2/11 (18%)**
	Low Valid ROI (<80%)[+] 10/27	Uninterpretable VTI[+] 1/27	Uninterpretable VTI[+] 7/21	Incomplete occlusion[+] 2/21	
	Noisy Signal[+] 3/27	Unstable Diameter 1/27	Unstable Diameter[+] 4/21	Other[+] 0/21	
		Other 0	Other[+] 0		
Successful Tests n/N (%)	25/27[+] (93%)	16/27[+] (59%)	26/27[+] (96%)	11/20[+] (55%)	19/21[+] (90%)
	Adverse Events n/N (%)				
Pain	1/14 (7%)				
Bruise	0 (0%)				
Functional Impairment	0 (0%)				
Others	0 (0%)				

FMD; Flow-mediated dilation, N; Total Number, NIRS; Near-infrared spectroscopy, VTI; Velocity-time integral

[+]Denominator is the total number of tests done without termination.

Table 4. Result of Feasibility Assessment in control group (n=21)

	ABI/TBI	PAT	Brachial FMD	Popliteal FMD	NIRS
Termination due to participant discomfort n/N (%)	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
Discomfort from cuff inflation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Duration of test	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Termination due to technical issue n (%)	**2 (9%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
Unable to find stable signal	2 (9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Program Error	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Uninterpretable Data n/N (%)	0 (0%)	**8/21 (38%)**	**1/21 (5%)**	**9/21 (43%)**	**0 (0%)**
		Low Valid ROI (<80%) 6	Uninterpretable VTI 1	Uninterpretable VTI 7	Incomplete occlusion 0
		Noisy Signal 2	Unstable Diameter 1	Unstable Diameter 2	Other[+] 0
			Other 0	Other 0	
Successful Tests n/N (%)	19/21 (90%)	13/21 (62%)	20/21 (95%)	12/21 (57%)	21/21 (100%)
			Adverse Events n/N (%)		
Pain			1/21 (5%)		
Bruise			0 (0%)		
Functional Impairment			0 (0%)		
Others			0 (0%)		

FMD; Flow-mediated dilation, N; Total Number, NIRS; Near-infrared spectroscopy, VTI; Velocity-time integral

[+]Denominator is the total number of tests done without termination.

Table 5. Comparison of Ankle- and toe-brachial index between groups.

	HD group (n=14)			**Control group (n=21)**
		Individuals who could not tolerate the cuff inflation (n=4)	Individuals who tolerated the cuff inflation (n=10)	
ABI	1.16 ± 0.16**	1.21 ± 0.20	1.15 ± 0.15	1.00 ± 0.07
TBI	0.83 ± 0.24*	0.69 ± 0.42	0.89 ± 0.10	1.02 ± 0.14
Ankle SBP (mmHg)	175 ± 45**	223 ± 22^{+}	155 ± 35	114 ± 14

ABI; Ankle-brachial index, HD; hemodialysis, TBI; Toe-brachial index, SBP; systolic blood pressure

*between patient vs. healthy controls. $p<0.05$.

**between patient vs. healthy controls. $p<0.01$

+between patient with and without discomfort. $p<0.05$

Table 6. Sub-group analysis individuals with uninterpretable PAT data in HD group

	Individuals with uninterpretable PAT (n=8)	Individuals without uninterpretable PAT (n=6)	p-value
ABI	1.10 ± 0.16	1.25 ± 0.11	0.06
TBI	0.73 ± 0.26	0.97 ± 0.08	<0.05

ABI; ankle-brachial index, TBI; toe-brachial index. Unpaired t-test between groups.

*p<0.05, unpaired t-test between groups

Table 7. Test-retest reliability analysis on NIRS/PAT data in HD group

	ICC	95% ICC	CV (%)	SEM	MDC	SD
	NIRS (n=9)					
$mVO2_{\%}$	0.96**	0.81-0.99	3.9	0.003	0.010	0.017
$T_{50\%}$	0.51	-0.33-0.88	20.6	3.5	9.6	4.9
$T_{baseline}$	0.68*	-0.03-0.93	22.8	3.5	9.8	6.2
$R_{recovery}$	0.56*	-0.12-0.89	16.5	0.078	0.216	0.118
$R_{baseline}$	0.84*	0.09-0.97	13.9	0.019	0.053	0.048
AUC_{2min}	0.70*	0.12-0.93	19.5	722	2001	1314
	PAT (n=5)					
RHI	0.20	-0.97-0.88	11.4	0.44	1.21	0.49
AI@75	0.95**	0.67-0.99	32.1	1.80	4.99	7.94

AI@75; augmentation index normalized to heart rate of 75 beats per minute, AUC; area under the curve, CV; coefficient of variation, ICC; Intraclass correlation coefficient, MDC; minimal detectable change, mVO2; muscle oxygen consumption, SD; standard deviation of differences, PAT; peripheral arterial tonometry, RHI; reactive hyperemia index, SEM; standard error of measurement.

* $p<0.05$, ** $p<0.01$

Table 8. Group comparison of NIRS/PAT result between HD and control group.

	HD group	Control group	P-value
	NIRS		
N	10	21	
Adipose tissue thickness (mm)	3.54 ± 0.85	3.69 ± 0.69	0.63
$mVO2_{\%}$ (%/s)	0.27 ± 0.05	0.20 ± 0.03	<0.01
$T_{50\%}$ (s)	11.8 ± 3.9	12.4 ± 4.2	0.69
$T_{baseline}$ (s)	23.6 ± 10.9	16.1 ± 5.6	0.06
$R_{baseline}$ (%/s)	3.8 ± 1.2	4.4 ± 1.4	0.76
$R_{recovery}$ (%/s)	4.1 ± 1.4	4.6 ± 1.8	0.44
AUC_{2min} (a.u)	3153 ± 1684	5515.8 ± 2406	<0.01
	PAT		
N	8	13	
RHI (a.u)	1.90 ± 0.39	1.76 ± 0.35	0.40
AI@75 (a.u)	17.66 ± 25.12	-13.18 ± 10.76	<0.05

AI@75; augmentation index normalized to heart rate of 75 beats per minute, AUC; area under the curve during hyperemia, $mVO2_{\%}$; muscle oxygen consumption percentage corrected, PA; popliteal artery, SR; shear rate, $T_{50\%}$; time taken to reach 50% max hyperemia, $T_{baseline}$; time taken to reach baseline $R_{baseline}$; recovery slope to baseline, $R_{recovery}$; recovery slope, RHI; reactive hyperemia index, VTI; velocity-time integral. Unpaired t-test between groups.

Table 9. Pearson correlation analysis between vascular parameters in HD group

	BA-FMD		PA-FMD		Finger PAT		NIRS					
	BA-FMD %/SR	**BA-VTI (cm)**	**PA-FMD %/SR**	**PA-VTI (cm)**	**Finger RHI (a.u)**	**Finger AI@75 (a.u)**	**mVO_2 %**	**$T_{50\%}$**	**$T_{baseline}$**	**$R_{recovery}$**	**$R_{baseline}$**	**AUC_{2min}**
BA-FMD%/SR												
BA-VTI (cm)	-0.28											
PA-FMD%/SR	0.36	-0.51										
PA-VTI (cm)	0.66	0.17	0.38									
Finger RHI (a.u)	0.24	0.11	0.37	0.86								
Finger AI@75 (a.u)	0.58	-0.38	**-0.98****	0.00	0.02							
$mVO_{2\%}$	**0.70***	-0.43	0.61	0.65	0.37	-0.35						
$T_{50\%}$	-0.04	-0.22	-0.02	-0.66	-0.15	0.02	-0.01					
$T_{baseline}$	0.39	-0.18	0.44	0.51	0.34	-0.59	**0.88****	0.12				
$R_{recovery}$	-0.07	0.25	-0.21	0.16	0.11	0.35	-0.63	**-0.62***	**-0.72***			
$R_{baseline}$	-0.48	0.13	-0.31	-0.45	-0.31	0.55	**-0.67***	-0.39	**-0.87****	**0.82****		
AUC_{2min}	0.17	0.1	-0.2	-0.2	0.65	0.36	-0.42	0.3	-0.35	0.36	0.13	

AI@75; augmentation index normalized to heart rate of 75 beats per minute, AUC; area under the curve during hyperemia, BA; brachial artery, FMD%; percentage flow-mediated dilation, $mVO2_{\%}$; muscle oxygen consumption percentage corrected, PA; popliteal artery, SR; shear rate, $T_{50\%}$; time taken to reach 50% max hyperemia, $T_{baseline}$; time taken to reach baseline $R_{baseline}$; recovery slope to baseline, $R_{recovery}$; recovery slope, RHI; reactive hyperemia index, VTI; velocity-time integral. *p<0.05, **p<0.01

Table 10. Pearson correlation analysis between vascular parameters in control group

	BA-FMD		**PA-FMD**		**Finger PAT**		**NIRS**					
	BA-FMD %/SR	**BA-VTI (cm)**	**PA-FMD%/SR**	**PA-VTI (cm)**	**Finger RHI (a.u)**	**Finger AI@75 (a.u)**	**mVO_2 %**	**$T_{50\%}$**	**$T_{baseline}$**	**$R_{recovery}$**	**$R_{baseline}$**	**AUC_{2min}**
BA-FMD%/SR												
BA-VTI (cm)	-0.26											
PA-FMD%/SR	0.45	0.11										
PA-VTI (cm)	-0.36	-0.38	-0.51									
Finger RHI (a.u)	-0.08	0.25	-0.18	0.44								
Finger AI@75 (a.u)	0.14	-0.1	0.05	-0.17	-0.15							
$mVO_{2\%}$	-0.35	0.19	-0.28	0.08	0.35	-0.25						
$T_{50\%}$	-0.19	-0.09	-0.18	-0.33	-0.23	-0.17	0.34					
$T_{baseline}$	-0.21	0.06	-0.19	-0.02	-0.19	-0.35	0.36	**0.72****				
$R_{recovery}$	0.03	0.03	0.07	0.07	0.14	0.27	-0.09	**-0.66****	**-0.85****			
$R_{baseline}$	0.08	0.05	0.06	0.21	0.25	0.28	-0.1	**-0.85****	**-0.79****	**0.93****		
AUC_{2min}	**0.46***	-0.34	0.37	-0.13	0.29	-0.4	-0.02	-0.2	-0.41	0.27	0.17	

AI@75; augmentation index normalized to heart rate of 75 beats per minute, AUC; area under the curve during hyperemia, BA; brachial artery, FMD%; percentage flow-mediated dilation, $mVO2_{\%}$; muscle oxygen consumption percentage corrected, PA; popliteal artery, SR; shear rate, $T_{50\%}$; time taken to reach 50% max hyperemia, $T_{baseline}$; time taken to reach baseline $R_{baseline}$; recovery slope to baseline, $R_{recovery}$; recovery slope, RHI; reactive hyperemia index, VTI; velocity-time integral. *p<0.05, **p<0.01

Table 11. Pearson correlation analysis between vascular parameters in both HD and control group

	BA-FMD		**PA-FMD**		**Finger PAT**		**NIRS**					
	BA-FMD%/SR	**BA-VTI (cm)**	**PA-FMD%/SR**	**PA-VTI (cm)**	**Finger RHI (a.u)**	**Finger AI@75 (a.u)**	**mVO_{2}%**	**$T_{50\%}$**	**$T_{baseline}$**	**$R_{recovery}$**	**$R_{baseline}$**	**AUC_{2min}**
BA-FMD%/SR												
BA-VTI (cm)	**-0.66****											
PA-FMD%/SR	**0.48***	-0.28										
PA-VTI (cm)	**-0.48***	**0.51***	-0.43									
Finger RHI (a.u)	0.22	-0.06	0.14	0.29								
Finger AI@75 (a.u)	**0.73****	**-0.66****	-0.08	-0.33	0.1							
$mVO_{2\%}$	**0.62****	**-0.54****	0.33	-0.4	0.4	0.13						
$T_{50\%}$	-0.08	-0.08	-0.11	-0.44	-0.24	-0.21	0.08					
$T_{baseline}$	**0.42***	**-0.37***	0.25	-0.38	0.15	-0.18	**0.74****	**0.36***				
$R_{recovery}$	-0.14	0.21	-0.07	0.33	0.11	0.18	-0.29	**-0.63****	**-0.72****			
$R_{baseline}$	-0.15	0.1	-0.08	0.25	0.04	0.26	-0.27	**-0.71****	**-0.71****	**0.89****		
AUC_{2min}	-0.13	0.21	0.04	0.3	0.21	-0.38	**-0.41***	-0.07	**-0.49****	0.34	0.17	

AI@75; augmentation index normalized to heart rate of 75 beats per minute, AUC; area under the curve during hyperemia, BA; brachial artery, FMD%; percentage flow-mediated dilation, $mVO2_{\%}$; muscle oxygen consumption percentage corrected, PA; popliteal artery, SR; shear rate, $T_{50\%}$; time taken to reach 50% max hyperemia, $T_{baseline}$; time taken to reach baseline $R_{baseline}$; recovery slope to baseline, $R_{recovery}$; recovery slope, RHI; reactive hyperemia index, VTI; velocity-time integral. *p<0.05, **p<0.01

Table 12. Group comparison of brachial and popliteal flow-mediated dilation (FMD) results between HD and control group.

	HD group	Control group	P-value
	Brachial Artery		
N	n = 14	n = 21	
Baseline Diameter (mm)	4.64 ± 0.69	3.53 ± 0.62	**<0.01**
Peak Diameter (mm)	4.79 ± 0.69	3.93 ± 0.62	**<0.01**
Absolute Change (mm)	0.15 ± 0.04	0.30 ± 0.13	**<0.01**
Shear Rate to Peak AUC (a.u)	14201.8 ± 6806.8	33972.8 ± 11229.6	**<0.01**
FMD$_{\%}$(%)	3.39 ± 0.93	8.76 ± 4.05	**<0.01**
FMD%/SR AUC (a.u)	0.028 ± 0.012	0.011 ± 0.005	**<0.01**
Allometric scaling coefficient β	0.966	0.921	**-**
Allometrically scaled FMD(%)	3.50 ± 1.05	9.68 ± 4.40	**<0.01**
VTI (cm)	51.7 ± 14.5	86.19 ± 14.81	**<0.01**
VRH (a.u)	0.93 ± 0.30	1.58 ± 0.30	**<0.01**
Baseline Velocity (cm/s)	16.2 ± 3.9	23.2 ± 7.7	**<0.01**
Peak Velocity (cm/s)	65.8 ± 16.6	97.5 ± 17.8	**<0.01**
Baseline Blood flow (ml/min)	283.5 ± 103.4	239.6 ± 135.6	**0.29**
Peak Blood flow (ml/min)	1149.5 ± 492.7	956.3 ± 406.1	**0.24**
	Popliteal Artery		
	n = 11	n = 20	
Baseline Diameter (mm)	5.35 ± 0.65	5.08 ± 0.95	**0.37**
Peak Diameter (mm)	5.61 ± 0.64	5.41 ± 0.97	**0.51**
Absolute Change (mm)	0.26 ± 0.10	0.33 ± 0.12	**0.11**
Shear Rate to Peak AUC (a.u)	10133.8 ± 3748.2	17711.8 ± 9080.7	**<0.01**
FMD$_{\%}$ (%)	5.19 ± 1.94	6.51 ± 2.56	**0.13**
FMD%/SR AUC (a.u)	0.062 ± 0.038	0.043 ± 0.029	**0.21**
Allometric scaling coefficient β	0.93	0.97	**-**
Allometrically scaled FMD(%)	5.57 ± 2.31	7.01 ± 2.72	**0.14**
VTI (cm)	48.8 ± 9.9	74.3 ± 14.5	**<0.01**
VRH (a.u)	0.70 ± 0.14	1.21 ± 0.28	**<0.01**
Baseline Velocity (cm/s)	12.8 ± 4.9	10.6 ± 3.5	**0.20**
Peak Velocity (cm/s)	52.02 ± 17.4	68.2 ± 20.3	**<0.05**
Baseline Blood flow (ml/min)	288.0 ± 166.5	216.5 ± 89.6	**0.23**
Peak Blood flow (ml/min)	1102.4 ± 441.6	1418.8 ± 652.6	**0.15**

AUC; area under the curve, FMD%; flow-mediated dilation, FMD%/SR AUC; flow-mediated dilation normalized to shear rate area under the curve to peak VTI; velocity-time integral, VRH; velocity of reactive hyperemia.

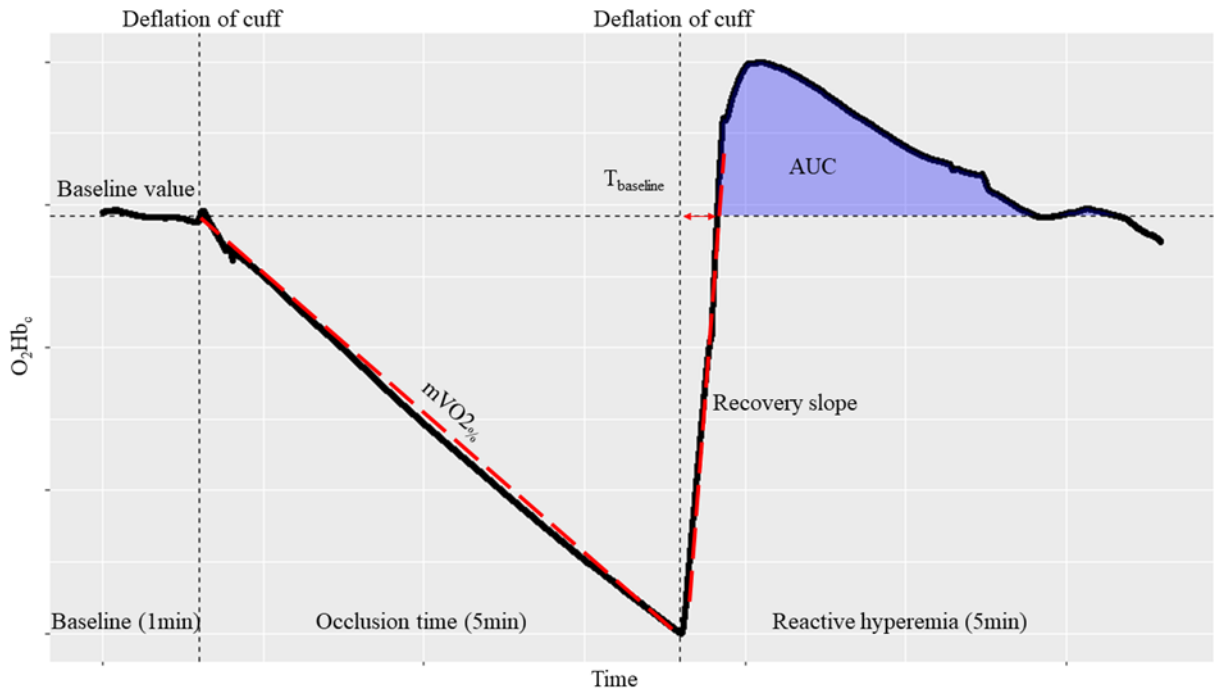

Figure 1. Example of a volume-corrected NIRS signal during the arterial occlusion test. AUC; area under the curve during the reactive hyperemia, $mVO_{2\%}$; muscle oxygen consumption slope, O_2Hb_c; volume-corrected oxyhemoglobin signal, $T_{baseline}$; time taken to reach baseline value during reactive hyperemia

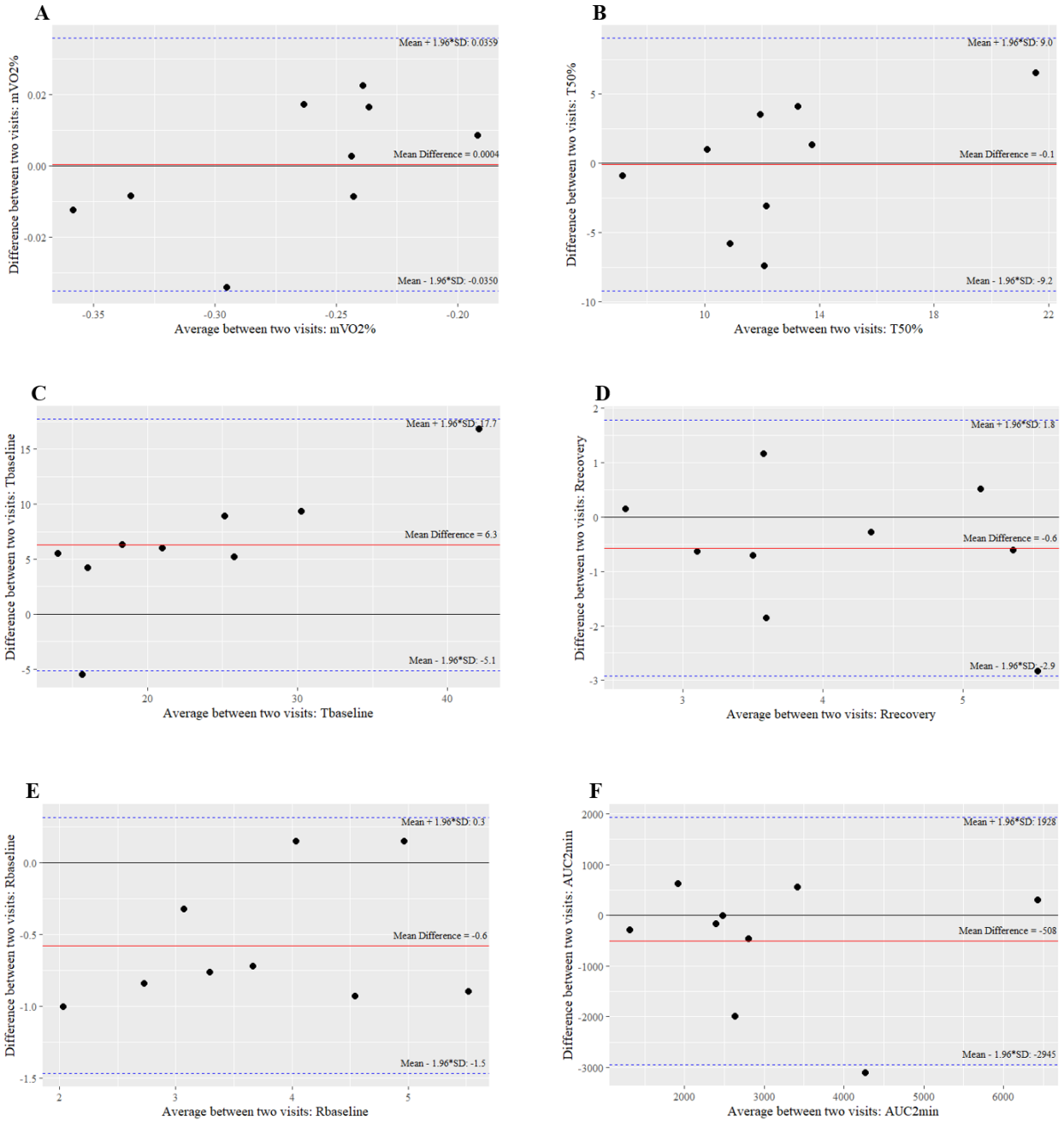

Figure 2. Bland-Altman plots of NIRS (panel A-F) parameters between two visits in HD group. The red line represents the mean difference between two visits. The blue dotted lines present upper, and lower limits of agreement (95%). The black line in the center represents zero. A) $mVO2_{\%}$; muscle oxygen consumption, B) $T_{50\%}$; time taken to reach 50% max hyperemia, C) $T_{baseline}$; time taken to reach baseline oxygenation, D) $R_{recovery}$; recovery slope, E) $R_{baseline}$; recovery slope to baseline, F) AUC_{2min}; area under the curve of 2 minutes hyperemic response.

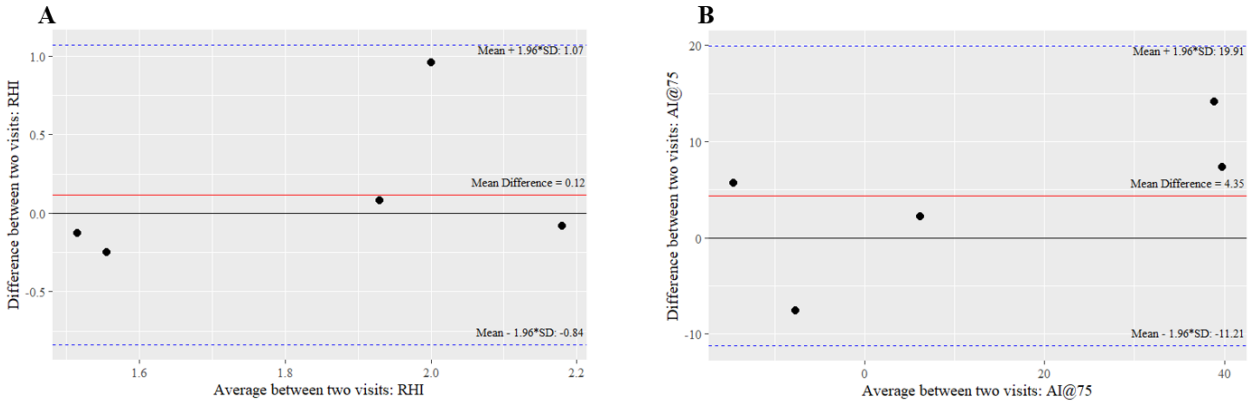

Figure 3. Bland-Altman plots of PAT (panel A-B) parameters between two visits in HD group. The red line represents the mean difference between two visits. The blue dotted lines present upper, and lower limits of agreement (95%). The black line in the center represents zero. A) RHI; reactive hyperemia index, B) AI@75; augmentation index normalized to heart rate of 75 beats per minute.

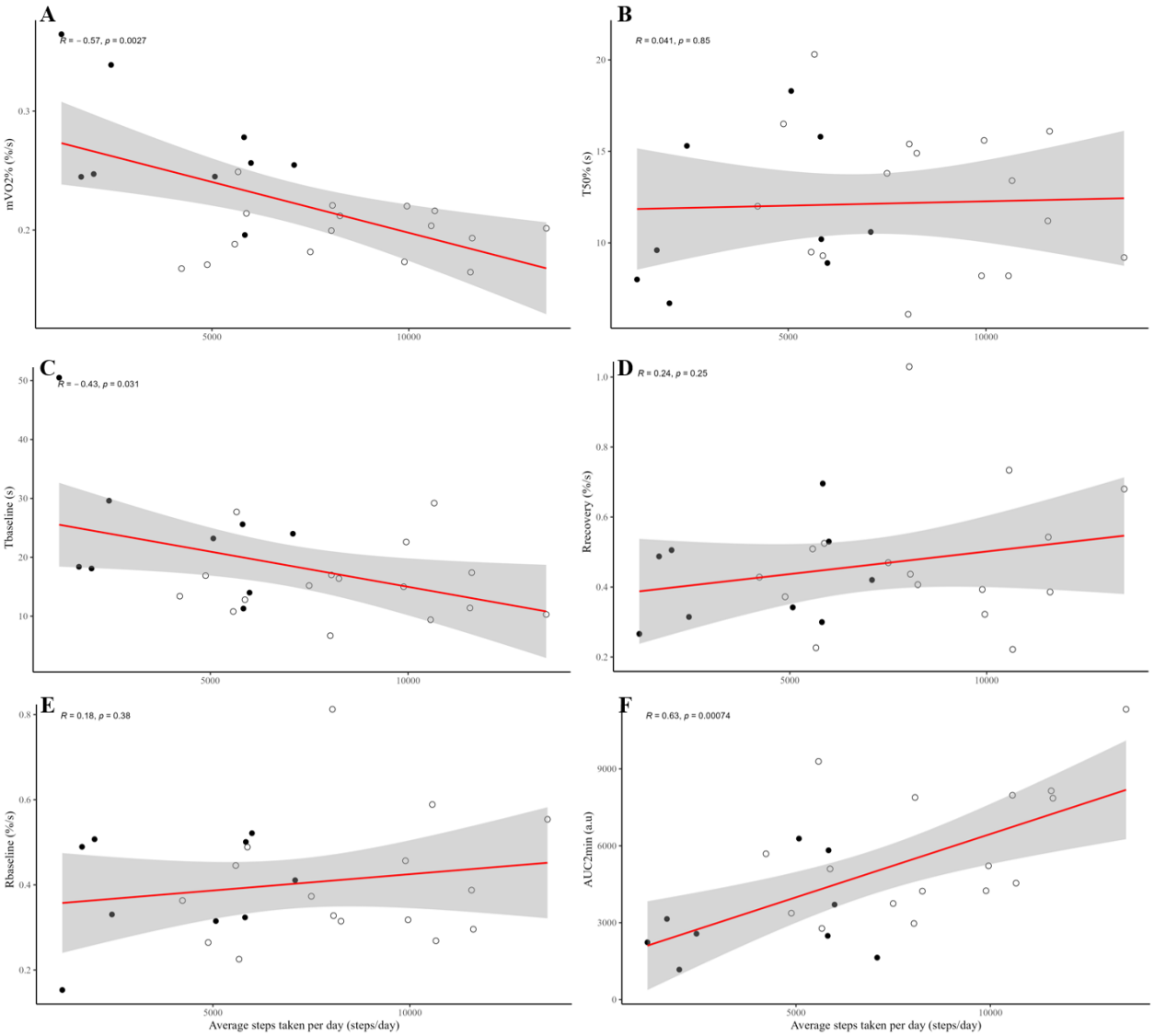

Figure 4. Pearson correlation analysis between NIRS parameters (y-axis) and the physical activity level (x-axis) in all individuals. The red line represents the linear regression line while the grey area shows the confidence interval of 95%. A) $mVO2_{\%}$; muscle oxygen consumption, B) $T_{50\%}$; time taken to reach 50% max hyperemia, C) $T_{baseline}$; time taken to reach baseline oxygenation, D) $R_{recovery}$; recovery slope, E) $R_{baseline}$; recovery slope to baseline, F) AUC_{2min}; area under the curve of 2 minutes hyperemic response. ●; HD group, ○; control group, R; Pearson correlation coefficient.

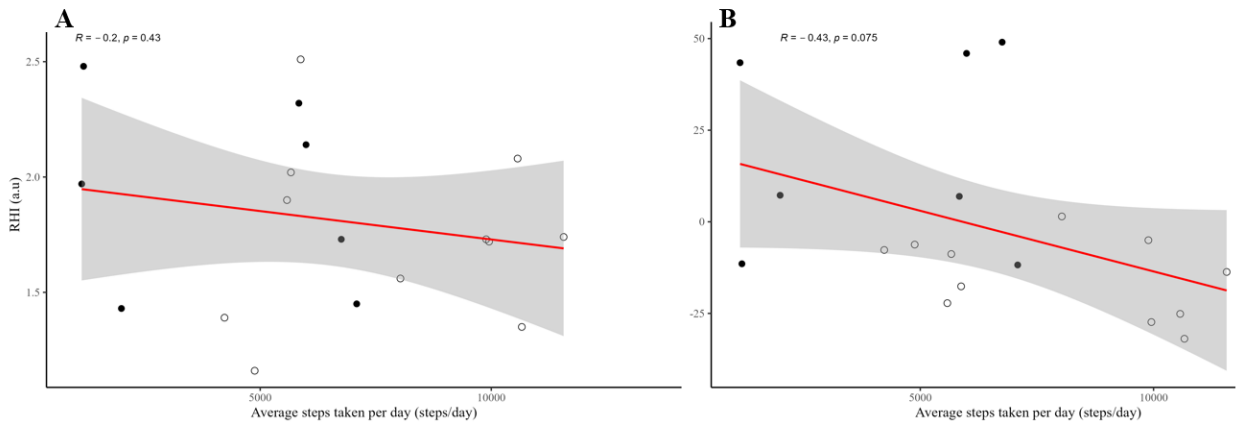

Figure 5. Pearson correlation analysis between PAT parameters (y-axis) and the physical activity level (x-axis) in all individuals. The red line represents the linear regression line while the grey area shows the confidence interval of 95%. The black line in the center represents zero. A) RHI; reactive hyperemia index, B) AI@75; augmentation index normalized to heart rate of 75 beats per minute. ●; HD group, ○; control group, R; Pearson correlation coefficient.

Chapter IV: General Discussion

4.1 General Discussion

Correlation between microvascular parameters (NIRS/PAT/VTI)

The mVO_2 is a surrogate marker of the peripheral oxygen extraction function of the muscle.[1] The peripheral oxygen consumption is determined by the mitochondrial mass and capillary density, and it is shown to be elevated in the individuals with PAD.[2] It is suggested that the extraction capacity is increased to compensate for decreased O_2 delivery from impaired vascular perfusion.[3,4] Such adaptations include the expansion of the mitochondrial mass, which is proposed to be an early manifestation of microvascular endothelial dysfunction.[5] The elevated mVO_2, which is indicative of this maladaptive response of skeletal muscle, has been consistently observed across varying severities of PAD, as reported by Malagoni et al.[2]. Similar trends have been noted in dialysis-dependent populations.[6] Our study's findings are congruent with this observation, with $mVO_{2\%}$ being significantly higher in the HD group compared to the healthy control group (0.27 ± 0.05 vs. 0.20 ± 0.03 %/s, $p<0.01$). In this manner, we observed moderate correlation between $mVO_{2\%}$ and BA-VTI ($r=0.54$, $p<0.01$), a proxy measure of microvascular function.[7]

In our study, we observed a trend suggesting that individuals in the HD group took a longer time to reach baseline oxygenation ($T_{baseline}$) compared to the control group. Although this trend did not reach statistical significance (23.6 ± 10.9 vs. 16.1 ± 5.6 seconds, $p=0.06$), it aligns with known characteristics of impaired kidney function and its effects on capillary rarefaction and density reduction.[8] The delayed recovery of NIRS parameters seen in individuals with PAD, as demonstrated by Kragelj et al.[9], was congruent in our findings. Additionally, the correlation we observed between $T_{baseline}$ and BA-VTI ($r=-0.37$, $p=0.04$) suggests that $T_{baseline}$ may serve as an indicative measure of an individual's microvascular function.

Our findings show contrasting trends for different PAT-measured parameters. The RHI, a measure of microvascular function, was not significantly different in the HD group compared to the control group (1.90 ± 0.39 vs.1.76 ± 0.35, p=0.40). The mechanisms underlying these variable RHI outcomes remain elusive, but several potential pathways may be implicated. For instance, the activity of endothelium-derived hyperpolarizing factor might be increased as a compensatory response to reduced NO bioavailability.[10,11] Alternatively, the myoendothelial feedback circuit, which regulates microvascular tone, could be disrupted by the documented imbalances of Ca^{2+} and K^{+} imbalances in ESKD.[12]

FMD is a well-validated measure of vascular endothelial function, primarily reflecting NO-dependent vasodilation of conduit arteries.[13] On the other hand, RHI, derived from PAT, is also thought to assess the microvasculature and endothelial function, but it is suggested to be less influenced by NO release.[14,15] While the association between FMD and RHI is controversial[16-18], the lack of correlation in our study suggests that there are different physiological mechanisms behind those vascular parameters despite their prognostic value.

In contrast, the augmentation index normalized at a heart rate of 75 (AI@75), a measure of arterial stiffness, was significantly higher in the HD group compared to the control group (17.66 ± 25.12 vs. -13.18 ± 10.76 a.u, $p<0.05$). While Antonopoulos et al.[19] previously demonstrated that arterial stiffness operates independently from the presence or progression of microvascular dysfunction, our findings indicate a potential association between arterial stiffness and microvascular dysfunction in individuals with ESKD. Given that high arterial stiffness is associated with an increased risk of amputation[20], assessing arterial stiffness could provide additional information for risk stratification in this population. However, more research is needed to further explore these relationships and their clinical implications.

Test-retest reliability of NIRS/PAT parameters

To our knowledge, this is the first study that presents the test-retest reliability of NIRS parameters in the dialysis-dependent ESKD population. Our results can thus only be compared with previous studies that examined similar clinical populations or healthy individuals.

First, our findings of high ICC (0.96) and CV (3.9%) for resting $mVO2_{\%}$ between two visits in the HD group are consistent with a previous study that examined a population with coronary heart disease (ICC=0.98, CV=7.92%).[21] Other studies with healthy populations reported a range of test-retest reliability. For example, Lucero et al.[22] reported moderate ICC (0.58) and high CV (50.4%) in the vastus lateralis muscles, while Southern et al.[23] reported within-subject reliability of $mVO2_{\%}$ with CVs ranging between 11.7-17.1% and ICCs ranging between –0.30 and 0.60 in the gastrocnemius. The Bland-Altman analysis of NIRS parameters was challenged by the lack of standardization of NIRS techniques in the previous studies. Therefore, our criteria on limits of agreements were evaluated by surrogate parameters from studies with different NIRS device manufacturers and/or signal processing techniques. The Bland-Altman analysis on $mVO2_{\%}$ showed a mean bias of 0.0004 between two visits, which can be converted to 0.024% per minute. This mean difference of $mVO2_{\%}$ is similar to the estimated mean difference (0.027%) between two visits in healthy young individuals[24], suggesting $mVO2_{\%}$ as a reliable measure in the dialysis-dependent ESKD population.

The reliability of recovery parameters in our study was also comparable to that reported by Lacroix et al.[25], which noted moderate ICCs in $T_{50\%}$ (0.63) and $R_{recovery}$ (0.59). When we confined the recovery curve analysis to the baseline point ($T_{baseline}$ and $R_{baseline}$), the reliability showed signs of improvement. Though $T_{baseline}$ had a moderate ICC, it was better than T50% (0.64 vs. 0.51), while $R_{baseline}$ presented a good ICC (0.84). The improved consistencies in $T_{baseline}$

and $R_{baseline}$ might be attributed to the nature of oxygenation recovery post cuff deflation. As pointed out by Bopp et al.[26], the recovery slope measured by NIRS best fits a sigmoidal function, featuring a rapid acceleration phase in the middle, followed by a plateau. Even though we did not specifically fit a sigmoidal function for each individual, the parameters to baseline value ($T_{baseline}$ and $R_{baseline}$) represent the rapid acceleration phase prior to reaching the plateau.

In contrast to the NIRS parameters, the RHI, as measured by PAT, exhibited a less satisfactory ICC (0.20) between the two visits, with a minimal detectable change of 1.21 (a.u). In comparison, a prior study by Liu et al.[27] reported a moderate ICC (0.74) within the dialysis-dependent cohort. Despite the PAT being done in the side of the arm without vascular access in our study, the calculation process inevitably involves the comparison of signals from both arms. Therefore, the disparity in ICCs may be attributed to the prevalence of vascular access in our study sample, where four out of the five participants included in the analysis had vascular access. In contrast, Liu et al.[27] opted to exclude these cases due to potential impacts on result accuracy. Conversely, the AI@75 showed excellent consistency with an ICC of 0.95. This finding aligns with previous studies conducted in different populations, which reported good to excellent ICCs ranging from 0.84 to 0.98.[28,29]

Assessing test-retest repeatability in a dialysis-dependent population presents inherent challenges. While NIRS cannot differentiate between myoglobin and hemoglobin signals, myoglobin's contribution to the NIRS signal is often neglected as it is generally considered to be minimal, and less than 10%.[30] However, it is worth noting that under certain conditions that alter skin or muscle blood flow, myoglobin's contribution to the NIRS signal can vary significantly.[31-33] Thus, any factors affecting skin temperature, muscle or subcutaneous blood flow may affect the reliability of NIRS signal with altered contribution of myoglobin in the tissue. In addition,

NIRS signals can be influenced by skin perfusion.[34] In our study, we did not measure individuals' total body water content- a factor that could have influenced reliability between visits. Furthermore, the PAT parameters (RHI and AI@75) are known to correlate with daily systolic blood pressure, especially in individuals with hypertension.[35] In our study, day-to-day blood pressure variability was observed in some individuals but was not accounted for in the analysis. The good to excellent levels of reliability have implications for the routine use of NIRS-based tests to improve diagnosis and management of peripheral vascular dysfunction in the individuals with ESKD.

4.2 Strengths and Limitations

Fluid overload is a common complication in individuals with reduced kidney function. The level of edema may affect the accuracy of NIRS signal as edema increases the distance between the skin where the NIRS probe is located and the blood capillaries that we are interested in. The level of interstitial fluid can increase the distance and ultimately affect the path length of photons emitted by NIRS, which is estimated to be half of the source-detector distance.[36] Our setup ensured a penetration depth of 20-25mm, and minimized potential signal contamination by subcutaneous adipose tissue.[37] Our region of interest (Tibialis anterior muscle) has relatively lower variations in adipose tissue thickness compared to other muscles, ranging a minimal 3.54 ± 0.85mm in the HD group. However, the presence of edema increases the distance between the skin and the capillaries additive to the adipose tissue thickness. We did not have any objective measure on the level of edema or fluid retention on the days of each visit.

We did not have any objective measure on the presence or level of each individual's arterial stenosis. The formation of turbulent flow downstream of a stenotic artery segment can result in elevated systolic velocity[38], which may potentially impact the accuracy of velocity signals obtained via Doppler ultrasound. Additionally, we did not account for the menstrual cycle phase in female participants. The intra-individual variability inherent in the menstrual cycle's effects on endothelial function is well-documented.[39] However, considering the age and low number of females in the HD group, its influences on the test-retest reliability of the NIRS/PAT parameters may be negligible.

Our participant cohort comprised individuals from a diverse range of racial and ethnic backgrounds, which we consider a strength of our study. This diversity ensures an applicability to a wide demographic and enhances the generalizability of our feasibility outcomes in this clinical population. However, it should be noted that our study included a total of fourteen individuals with dialysis-dependent ESKD. It remains uncertain how our results may change once we achieve our planned sample size of 40 individuals. Future research aimed at examining the diagnostic accuracy of NIRS/PAT-based vascular tests could draw upon our findings, as they provide preliminary data needed for study planning.

4.3 Future Directions

Exercise imposes substantial physiological demand on the cardiovascular system, assessing the physiological responses to exercise can yield valuable insights into one's cardiovascular health. NIRS measurements conducted during exercise are minimally invasive, and have shown its potential in examining the microvascular function.[33] Intradialytic cycling, a potential intervention that is generally well-tolerated, is suggested to enhance an individual's quality of life, exercise capacity, and cardiovascular parameters.[40] Incorporation of NIRS during

the cycling exercise may provide information on vascular function under demand, and could potentially alleviate the tolerance issues in our study, specifically those related to discomfort from arterial occlusion.

Each dialysis session can be appraised by the HD adequacy. Similar to the challenges from fluid overload or retention, we did not evaluate the adequacy of the HD session that was held prior to the lab visit. In other words, the fluid level in each individual could have been different between the visits, introducing a potential source of variability into our results. To enhance the clinical applicability of our findings, future investigations will need to evaluate the impact of HD adequacy on NIRS/PAT parameters.

A longitudinal research approach could further elucidate the clinical implications of impaired NIRS/PAT parameters. For instance, examining the association between changes in the NIRS/PAT parameters with dialysis adequacy may provide valuable information in predicting the future risks of developing lower-limb complications. Moreover, the integration of NIRS testing with other modalities, such as nailfold capillaroscopy, angiography, or transcutaneous oximetry, could provide a more comprehensive evaluation of one's microvascular function.

Appendices

Appendix A: Participant eligibility criteria

	Inclusion	Exclusion
HD group	- ≥18 years old - At least one upper & lower limb available for measurements -Able to lie supine & semi-prone - No contraindications to ischemic occlusion of the limb - HD starts within previous 6 months or eGFR less than 15ml/min over the past 6 months	- Unable to provide informed consent - Acute kidney injury and requires recovery of kidney function (physician decision) - Presence of critical limb ischemia - Hypoxic digit (SpO2 <92%) - Absence of sensation in the lower limbs - Unable to transfer to bed from a chair
Healthy controls	- ≥18 years old - Non-smokers without history or symptoms of cardiovascular disease - No diabetes or kidney disease - Resting BP less than 130/80	- Unable to provide informed consent

Appendix B: Detailed calculations of Ankle-brachial Index & Toe-brachial Index

The systolic pressures measured in brachial artery on each side are averaged. The higher pressure between the left and right arm is used as a denominator. For the ankle systolic pressure, the higher average value among two different sites (dorsalis pedis and posterior tibialis artery pressure) is used as a numerator for ABI calculation.[41]

$$ABI = \frac{Higher\ ankle\ SBP\ (Dorsalis\ pedis\ or\ Posterior\ tibialis)}{Higher\ brachial\ SBP}$$

For TBI calculations, the average values of each side were used as numerators.[42]

$$TBI = \frac{Average\ toe\ SBP}{Higher\ brachial\ SBP}$$

Appendix C: Detailed calculations of Reactive Hyperemia Flow-mediated Dilation

The changes in arterial diameter during the reactive hyperemia compared to the baseline values is referred to as FMD%. A 1% increase in FMD% is associated with a 9% decrease in CV risk.[43] FMD% is calculated as the following formula:

$$FMD\% = [(peak\ diameter - baseline\ diameter)\ /\ baseline\ diameter] \times 100$$

Shear rate of the blood flow was also automatically calculated at each second by the same software with the following formula:

$$Shear\ rate\ (/s) = 4 \times mean\ velocity/mean\ diameter^{44}$$

The incremental area under the curve of shear rate (AUC_{shear}) until time to reach the peak diameter was calculated using the trapezoid method.[45] The magnitude of shear rate is considered as a crucial regulator of FMD, and therefore FMD response is normalized using the following formula and expressed in an arbitrary unit[46]:

$$FMD\%_{shear}(A.U) = \frac{FMD\%}{AUC_{Shear}} \times 100$$

Allometric scaling is another approach to correct FMD% by removing the statistical bias imposed by the baseline diameter.[47] The following formula was used for individual scaling of FMD:

$$FMD\%_{allometric} = \frac{Peak\ diameter - Baseline\ diamaeter}{Baseline\ diameter^{b}} \times 100$$

The correctional allometric exponent or *b* is calculated as the slope of the relationship between log-transformed baseline diameter and log-transformed peak diameter.[48]

The blood flow at each second was calculated using the following formula:

$$Blood\ flow\ (ml/min) = mean\ velocity\ \times\ \pi\ \times\ radius^2$$

The microvascular parameter, VTI was calculated as the area under curve of the first hyperemic heartbeat's velocity profile following cuff release. Velocity during the reactive hyperemia (VRH) is VTI normalized to each individual's heart rate measured with PAT during the BA-FMD test, and calculated as the following:

$$VRH\ (cm/s) = VTI\ \times Heart\ rate\ /\ 60$$

It has been suggested that this assessment tool may be more sensitive than using FMD therefore may be able to detect earlier consequences of cardiovascular risk factors.[49]

Appendix D: Detailed calculations of Near-Infrared Spectroscopy

The recorded NIRS data were zeroed based on the baseline value 30-seconds prior to the cuff inflation. The baseline, minimum and maximum values of changes for each hemoglobin concentration were recorded in micromolars per second (μM/s). Temporal parameters during the recovery were calculated as the time taken to reach 1) half to max/min value, 2) 95% to max/min value, and 3) max/min values, and reported in seconds. The absolute muscle O_2 consumption (mVO_{2abs}) during the arterial occlusion is corrected to the blood volume change.[50] At each second, a correction factor β was calculated as the following:

$$\beta(t) = \frac{|O_2Hb(t)|}{(|O_2Hb(t)| + |HHb(t)|)}$$

Once the correction factor β at each time point, the raw O2Hb and HHb data are corrected as the following:

$$O_2Hb_c = O_2Hb - [tHb \times (1 - \beta)]$$

$$HHb_C = HHb - (tHb \times \beta)$$

During arterial occlusion, a closed system is created in the tissue of interest under NIRS probe. Therefore, the rate of increase in HHb, or decrease in O2Hb are translated to the rate of local O2 consumption. The blood volume corrected concentration changes (O_2Hb_c, HHb_c) at each second (μM/s) were converted to millimeters O_2 per minute per 100 gram tissue (mlO_2/min/100g). Assuming standard temperature (0°C or 273 K), pressure (760 mm Hg), and dry (no water vapor) condition, the molar volume of gas is 22.4 L, and four O2 molecules are bound to each hemoglobin molecule. Using a value of 1.04 kg/L as muscle density, the mVO_{2abs} during the arterial occlusion was calculated as the following:

$$mVO_{2abs} = \left|\left(\left(\frac{\Delta O_2Hb_C \times 60}{10 \times 1.04}\right) \times 4\right)\right| \times \frac{22.4}{1000}\ in\ mlO_2 \cdot min^{-1} \cdot 100g^{-1}$$

The changes in first 60 seconds of occlusion were used for ΔO2Hb.[1] After the blood volume correction, the ΔO_2Hb_c is interchangeable with ΔHHb_c.[50] While using a constant DPF, the mVO_{2abs} during the arterial occlusion was also corrected using the physiological calibration method.[37] The ΔO_2Hb_c signal at the end of cuff occlusion were used as a reference point of 0%, while the subsequent peak values during the hyperemia were regarded as 100%. The physiologically calibrated signal ($O_2Hb_{\%}$) were analyzed and expressed as in percentage change per second (%/s). Therefore, the relative local muscle oxygen consumption ($mVO_{2\%}$) is calculated as the slope of change in $O_2Hb_{\%}$ during the arterial occlusion using simple linear regression.

The NIRS parameters were collected during hyperemia or recovery from the arterial occlusion. The magnitude of hyperemic response was evaluated by calculating the area under the curve (AUC) of O_2Hb_c two- and five-minutes following the cuff deflation using the trapezoid method. The series of reperfusion slopes (%/s) were evaluated at different segments including the total recovery ($R_{100\%}$), 95% ($R_{95\%}$), 75%($R_{75\%}$), 50% ($R_{50\%}$), to baseline value ($R_{baseline}$), and 10 seconds following occlusion (R_{10sec}). The time taken to reach each recovery magnitude was also evaluated; half-time recovery ($T_{50\%}$), 95% recovery ($T_{95\%}$), max recovery ($T_{100\%}$), and time to reach baseline value from pre-occlusion ($T_{baseline}$) were calculated and expressed in seconds.

Appendix E: Detailed calculations of Near-Infrared Spectroscopy Measurement and analysis of NIRS parameters during post-occlusive reactive hyperemia

Parameter	Unit	Time envelope	Calculation
O_2Hb_c	µM/s	Entire Signal	Corrected to blood volume change based on the factor β^{50}
$O_2Hb_{\%}$	%/s		Physiologically calibrated O_2Hb_c signal based on maximal hyperemia response (100%) and maximal ischemic response (0%)
mVO_{2abs}	ml O_2/min /100 g	Occlusion	$\lvert((\Delta O2Hb \cdot 60)/(10 \cdot 1.04)) \cdot 4) \cdot 22.4 \cdot 1000^{-1}\rvert$ Absolute muscle O_2 consumption
$mVO_{2\%}$	%/s		Decrease rate of O_2Hb during occlusion calibrated by maximal hyperemia response (100%) and maximal ischemic response (0%)
$T_{50\%}$	Second (s)	Hyperemia	Time taken to reach 50% of max hyperemia
$T_{baseline}$	Second (s)		Time taken to reach baseline resting value during hyperemia
$R_{recovery}$	%/s		Linear slope to reach 100% of max hyperemia from the end of occlusion
$R_{baseline}$	%/s		Linear slope from the end of occlusion for 10 seconds
AUC_{2min}	a.u		Area under curve of hyperemic response of O_2Hb_c above baseline for 2 minutes

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